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CANADA COMMUNICABLE DISEASE REPORT

MULTIDRUG-RESISTANT GONORRHEA

Surveillance

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Commentary

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CANADA COMMUNICABLE DISEASE REPORT

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The cover photo shows a woman with body language consistent with pelvic inflammatory disease. This could be caused by gonorrhea infection that was either untreated or resistant to treatment. Adapted from photo by Shutterstock (https://www.shutterstock.com/image-vector/young-beautiful-woman-having-abdominal-pain-497547358).

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CANADA COMMUNICABLE DISEASE REPORT

MULTIDRUG-RESISTANT GONORRHEA

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Multidrug-resistant and extensively drug-resistant *Neisseria gonorrhoeae* in Canada, 2012–2016

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Abstract

Background: *Neisseria gonorrhoeae* have acquired resistance to many antimicrobials, including third generation cephalosporins and azithromycin, which are the current gonococcal combination therapy recommended by the *Canadian Guidelines on Sexually Transmitted Infections.*

Objective: To describe antimicrobial susceptibilities for *N. gonorrhoeae* circulating in Canada between 2012 and 2016.

Methods: Antimicrobial resistance profiles were determined using agar dilution of *N. gonorrhoeae* isolated in Canada 2012–2016 (n=10,167) following Clinical Laboratory Standards Institute guidelines. Data were analyzed by applying multidrug-resistant gonococci (MDR-GC) and extensively drug-resistant gonococci (XDR-GC) definitions.

Results: Between 2012 and 2016, the proportion of MDR-GC increased from 6.2% to 8.9% and a total of 19 cases of XDR-GC were identified in Canada (0.1%, 19/18,768). The proportion of isolates with decreased susceptibility to cephalosporins declined between 2012 and 2016 from 5.9% to 2.0% while azithromycin resistance increased from 0.8% to 7.2% in the same period.

Conclusion: While XDR-GC are currently rare in Canada, MDR-GC have increased over the last five years. Azithromycin resistance in *N. gonorrhoeae* is established and spreading in Canada, exceeding the 5% level at which the World Health Organization states an antimicrobial should be reviewed as an appropriate treatment. Continued surveillance of antimicrobial susceptibilities of *N. gonorrhoeae* is necessary to inform treatment guidelines and mitigate the impact of resistant gonorrhea.

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Keywords: *Neisseria gonorrhoeae*, *N. gonorrhoeae* multidrug resistant, antimicrobial resistance, laboratory surveillance, STI, STBBI, sexually transmitted infections, sexually transmitted and blood-borne infections, gonorrhea, gonococcal infection

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Introduction

Gonorrhea is the second most commonly reported sexually transmitted infection in Canada, the causative organism being *Neisseria gonorrhoeae*. In 2016, 23,708 cases of gonorrhea were reported to the Public Health Agency of Canada (PHAC); rates had increased 87%, from 34.9 cases/100,000 population in 2012 to 65.4 cases/100,000 in 2016 (1). In 2016, 82% of the total reported cases of gonorrhea in Canada occurred in the 15–39 year age group and the highest rates among males were found among those aged 20–29 years and among females aged 15–24 years (2). Globally, there are an estimated 78 million cases of gonorrhea infection occurring per year (3). Treatment is complicated, as *N. gonorrhoeae* have acquired resistance mechanisms to many of the antimicrobials used for treatment over the years (4). This resistance has been documented by surveillance programs that are used to support appropriate treatment recommendations.

A challenge to gonococcal (GC) surveillance programs is that the number of cultures available for antimicrobial susceptibility testing is on the decline due to the shift from the use of bacterial culture to nucleic acid amplification test (NAAT) for the diagnosis of gonorrhea. This is of concern as *N. gonorrhoeae* cultures are also required for antimicrobial susceptibility testing. Currently almost 80% of gonococcal infections in Canada are now diagnosed using NAAT (5). Some jurisdictions in Canada no longer maintain the capacity to culture this organism and, therefore, antimicrobial susceptibility data in these jurisdictions are not available.

Canadian gonococcal surveillance data from 2012 reported an increase in isolates with decreased susceptibility to cephalosporins, prompting an update to the recommendation for gonorrhea treatment in the *Canadian Guidelines on Sexually Transmitted Infections* to combination therapy with two antibiotics. In uncomplicated anogenital infections and pharyngeal infections, ceftriaxone 250 mg intramuscularly (IM) plus azithromycin 1 g orally is currently recommended as a first-line treatment (6).

Along with rising antimicrobial resistance rates, there have also been reports of *N. gonorrhoeae* with high-level resistance and gonococcal treatment failures; all causes for concern. Treatment failures involving cefixime, a potent oral cephalosporin, have been reported internationally (7–12) as well as in Canada (13,14). Most of these cases were successfully treated with ceftriaxone (250 mg IM). In 2009, Japan identified an isolate (H041) that caused a pharyngeal treatment failure with ceftriaxone that showed unusually high minimum inhibitory concentrations (MICs) to ceftriaxone (2 mg/L) and cefixime (8 mg/L); treatment with ceftriaxone 1 g intravenously cleared the infection (15). More pharyngeal treatment failures to ceftriaxone were reported in Sweden (16,17), Slovenia (18) and Australia (19,20), which were then treated successfully with a higher dosage of ceftriaxone (1 g IM), azithromycin (2 g orally) or a combination of ceftriaxone (250 mg IM) and azithromycin (1 g orally). In 2011, France reported the first genital treatment failure to ceftriaxone in Europe (11). In 2014, the first dual antimicrobial therapy treatment failure was reported in the United Kingdom (UK) (ceftriaxone 500 mg plus azithromycin 1 g) and was successfully treated with ceftriaxone (1 g IM) plus azithromycin (2 g oral) (21). Since 2013, cases of ceftriaxone resistance have been identified and characterized in a number of countries, including Canada, Japan and Australia, which were successfully treated with azithromycin (22,23). The UK and Australia have also recently reported treatment failure cases due to high-level ceftriaxone resistance (MIC=0.5 mg/L) and high-level azithromycin resistance (MIC greater than or equal to 256 mg/L). The UK case was successfully treated with intravenous ertapenem (24).

Rising azithromycin resistance rates have also been reported in Canada (5) and internationally (25), which is of concern as azithromycin is part of the recommended combination therapy. Along with increasing moderate-level azithromycin resistance, there have been reports of high-level azithromycin resistance (MIC greater than or equal to 256 mg/L) that were associated with a large-scale outbreak in the UK (26). Although isolates with this high azithromycin MIC have been identified in Canada, a total of seven were identified between 2009 and 2016 (5); these cases appear to be sporadic occurrences in Canada and have not spread.

In 2009 (27), definitions were established for multidrug-resistant gonococci (MDR-GC) and extensively drug-resistant gonococci (XDR-GC), which we have recently updated, taking into account the *Canadian Guidelines on Sexually Transmitted Infections* and the antimicrobials being tested in our routine laboratory surveillance (**Text box 1**).

Text box 1: Definitions of multidrug-resistant gonococci (MDR-GC) and extensively drug-resistant gonococci (XDR-GC)

MDR-GC – decreased susceptibility/resistance to ***one*** currently recommended therapy (cephalosporin **OR** azithromycin) PLUS resistance to at least ***two*** other antimicrobials (penicillin, tetracycline, erythromycin, ciprofloxacin)

XDR-GC – decreased susceptibility/resistance to ***two*** currently recommended therapies (cephalosporin **AND** azithromycin) PLUS resistance to at least ***two*** other antimicrobials (penicillin, tetracycline, erythromycin, ciprofloxacin)

PHAC's National Microbiology Laboratory (NML), in collaboration with the provincial laboratories, has been monitoring the antimicrobial susceptibilities of *N. gonorrhoeae* since 1985. In this report, we present national-level trends in antimicrobial susceptibilities of *N. gonorrhoeae* collected from 2012 to 2016, applying the updated MDR-GC and XDR-GC definitions.

Methods

Between 2012 and 2016, *N. gonorrhoeae* cultures were submitted to the NML by provincial laboratories when they identified a resistant (R) isolate or by laboratories that did not conduct antimicrobial susceptibility testing (**Table 1**). Information regarding the isolates submitted to NML included sex and age of the patient, province/territory where infection was diagnosed, as well as the site of infection. Annually, each province/territory informs the NML of the total number of cultures collected and tested, either in their province/territory or at the NML (Table 1). These totals are used as the denominators in determining the proportions of antimicrobial drug resistance.

Antimicrobial susceptibilities of *N. gonorrhoeae* to azithromycin, cefixime, ceftriaxone, erythromycin, penicillin, spectinomycin, tetracycline, ciprofloxacin, ertapenem and gentamicin were determined using agar dilution (28). The MIC interpretative standards used were as recommended by the Clinical and Laboratory Standards Institute (28) except for erythromycin (R ≥ 2 mg/L) (29), azithromycin (R ≥ 2 mg/L) (30), ceftriaxone (DS ≥ 0.125 mg/L) and cefixime (DS ≥ 0.25 mg/L) (31), ertapenem (NS ≥ 0.063 mg/L) (32) and gentamicin (R ≥ 32 mg/L) (33,34). The *N. gonorrhoeae* reference cultures ATCC49226, WHOF, WHOG, WHOK, and WHOP/WHOU were used as controls. Statistical analysis was determined by using EpiCalc 2000 version 1.02 (www.brixtonhealth.com/epicalc.html).

A 2 × 2 χ^2 test was used to compare proportions of resistance per year to identify significant differences between years (p values calculated with 99% confidence intervals).

Table 1: *Neisseria gonorrhoeae* cultures collected by provinces and territories and sent to the National Microbiology Laboratory (NML), 2012–2016

Year	Cultured	BC[a]	AB[a]	SK[b]	MB[b]	ON[a]	QC[a]	NS[b]	Other[b,c]	Total cultures	Total cases reported in Canada	% of total cases tested by cultures
2012	Collected	372	497	57	49	1,218	838	0	5	3,036	12,561	24.20%
	Sent to NML[d]	92	93	57	8	396	383	0	4	1,033		
2013	Collected	454	514	69	29	1,404	716	1	8	3,195	13,786	23.20%
	Sent to NML[d]	170	135	67	7	498	298	1	8	1,184		
2014	Collected	492	468	91	46	1,767	918	15	12	3,809	16,285	23.40%
	Sent to NML[d]	335	323	91	46	849	400	14	12	2,070		
2015	Collected	602	793	62	48	1,673	986	13	13	4,190	19,845	21.10%
	Sent to NML[d]	387	512	65	44	1,076	531	13	10	2,638		
2016	Collected	600	786	86	85	1,735	1,197	32	17	4,538	23,708	19.10%
	Sent to NML[d]	348	695	85	81	1,068	927	31	7	3,242		
Total	Collected	2,520	3,058	365	257	7,797	4,655	61	55	18,768	86,185	21.80%
	Sent to NML[d]	1,332	1,758	365	186	3,887	2,539	59	41	10,167		

Abbreviations: AB, Alberta; BC, British Columbia; MB, Manitoba; NS, Nova Scotia; ON, Ontario; QC, Quebec; SK, Saskatchewan
[a] Province performs antimicrobial susceptibility testing and sends only primarily resistant isolates to the NML
[b] Province does not perform antimicrobial susceptibility testing (Manitoba stopped in 2014) and sends all cultures to the NML
[c] Other includes Northwest Territories, New Brunswick, Newfoundland and Prince Edward Island. Nunavut and the Yukon did not report or send any *N. gonorrhoeae* cultures to the NML from 2012 to 2016
[d] Numbers include only one culture/case

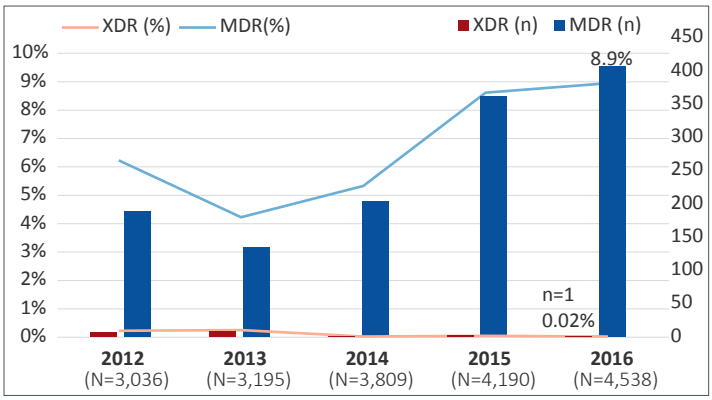
Results

From 2012 through 2016, 21.8% (n=18,768) of the 86,185 cases of *N. gonorrhoeae* infection reported in Canada (1) were diagnosed by culture. Provincial public health laboratories submitted 10,167 isolates to NML for testing (2012, n=1,033; 2013, n=1,184; 2014, n=2,070; 2015, n=2,638; 2016, n=3,242). Sex and age data of patients were available for 10,104 (99.4%) isolates. Of these, 8,649 (85.6%) were from male patients (median age 30 years; range less than 1–83 years) and 1,455 (14.4%) were from female patients (median age 26 years; range less than 1–71 years). Source specimens included urethral (n=4,836), rectal (n=2,100), pharyngeal (n=1,367), cervical (n=625), vaginal (n=249) and other sources (n=209); sources for 781 isolates were not given. The sexual orientation of patients and information on cases of treatment failure were not available.

Multidrug-resistant gonorrhea

The proportion of MDR-GC increased from 6.2% (n=189/3,036) in 2012 to 8.9% (n=406/4,538) (p<0.001) in 2016. These percentages represent the proportion of isolates with decreased susceptibility to the cephalosporins or resistance to azithromycin, along with resistance to two other antimicrobials (**Figure 1**).

Figure 1: Multidrug-resistant and extensively drug-resistant *Neisseria gonorrhoeae* isolates in Canada, 2012–2016[a]



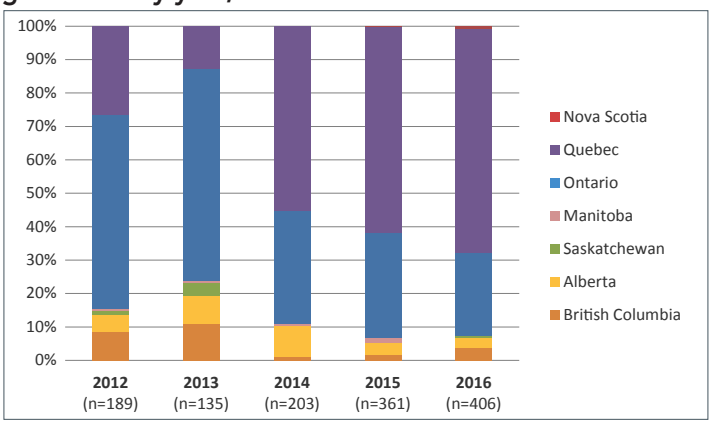
Abbreviations: MDR, multidrug-resistant gonococci; n, number; N, total number; XDR, extensively drug-resistant gonococci
[a]Percentages are based on the total number of isolates tested nationally per year

Provincial distribution of MDR-GC identified in Canada is represented in **Figure 2**, with the highest proportion identified in Quebec (67.0%), followed by Ontario (24.9%) in 2016. British Columbia, Alberta, Nova Scotia and Saskatchewan also identified cases of MDR-GC in 2016.

The temporal trends of MDR-GC within each province are displayed in **Figure 3**, and the provinces with the highest proportions of MDR-GC in 2016 were Quebec (22.7%) followed by Nova Scotia (9.4%) and Ontario (5.8%).

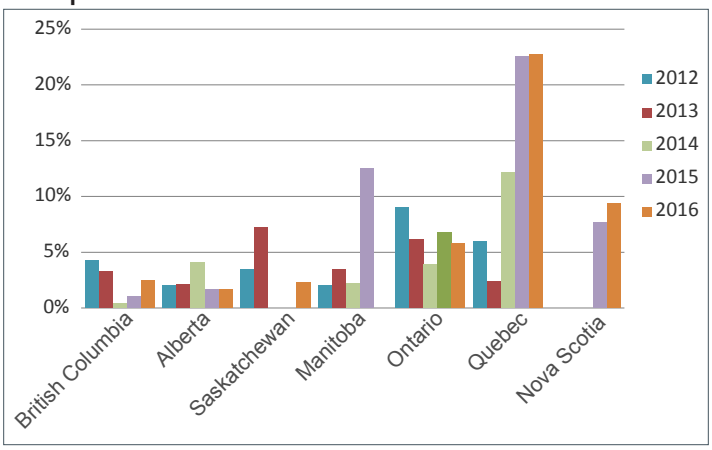
Figure 4 represents the trends of the antimicrobials associated with MDR-GC. The MDR-GC associated with azithromycin resistance increased significantly (p<0.001) from 9.5% in 2012 to 78.3% in 2016. Conversely, MDR-GC associated with decreased susceptibility to cefixime and ceftriaxone declined significantly (p<0.001) from 29.6% in 2012 to 1.2% in 2016.

Figure 2: Provincial distribution of multidrug-resistant gonococci by year, 2012–2016[a]



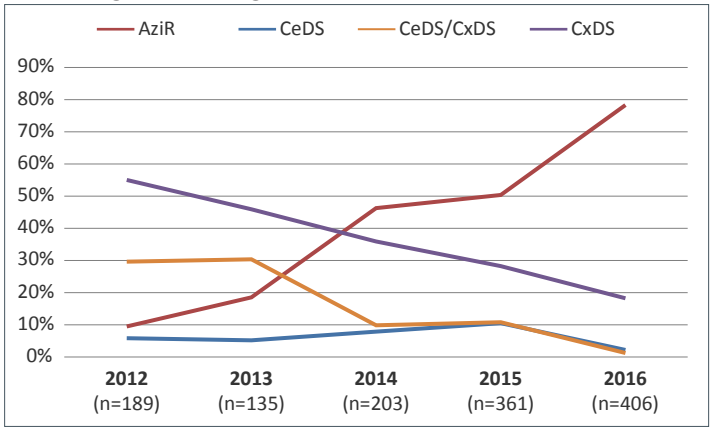
Abbreviation: n, number
[a] Percentages are based on the total number of multidrug-resistant gonococci identified each year

Figure 3: Proportion of multidrug-resistant gonococci in each province from 2012 to 2016[a]



[a] Percentages are based on the total number of cultures in each province

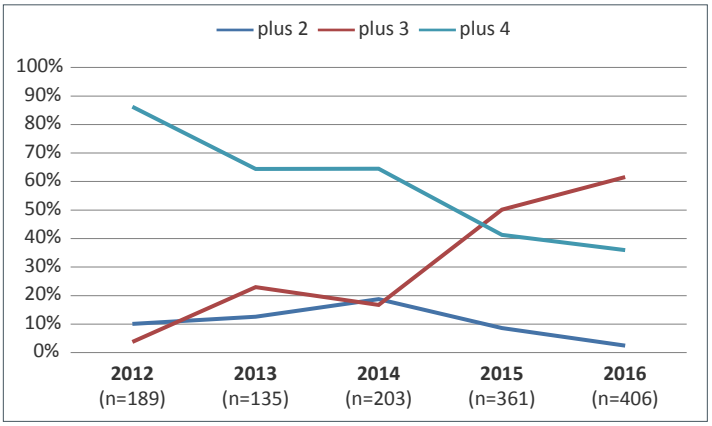
Figure 4: Trends of antimicrobials associated with multidrug-resistant gonococci, 2012–2016[a]



Abbreviations: AziR, azithromycin resistant; CeDS, decreased susceptibility to cefixime; CeDS/CxDS, decreased susceptibility to cefixime and ceftriaxone; CxDS, decreased susceptibility to ceftriaxone; n, number
[a] Percentages based on total number of multidrug-resistant gonococci per year

Figure 5 represents the trends of MDR-GC associated with resistance to two, three or four additional antimicrobials. The MDR-GC with resistance to three additional antimicrobials increased significantly (p<0.001) from 3.7% in 2012 to 61.6% in 2016 with ciprofloxacin, erythromycin and tetracycline as the most common co-resistance antimicrobials.

Figure 5: Trends of multidrug-resistant gonococci with resistance to two, three or four additional antimicrobials[a]



Abbreviations: n, number; plus 2, multidrug-resistant gonococci with resistance to two antimicrobials not recommended for therapy; plus 3, multidrug-resistant gonococci with resistance to three antimicrobials not recommended for therapy; plus 4, multidrug-resistant gonococci with resistance to four antimicrobials not recommended for therapy
[a] Percentages based on total number of multidrug-resistant gonococci per year

Extensively drug-resistant gonococci

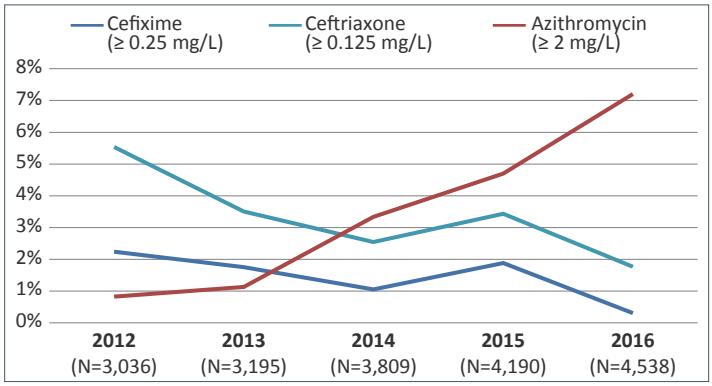
From 2012 to 2016, only 19 cases of XDR-GC were identified in Canada (0.1%, n=19/18,768). In 2012, seven XDR-GC isolates with combined decreased susceptibility to cephalosporins and resistance to azithromycin were identified (0.2%, n=7/3,036; Ontario n=6; British Columbia n=1), which increased to eight (0.3%, n=8/3,195; Ontario n=5; British Columbia n=2; Saskatchewan n=1) in 2013. From 2014 to 2016, however, XDR-GC numbers were lower: in 2014, only one was identified (0.03%, n=1/3,809; Quebec); in 2015, two were detected (0.05%, n=2/4,190; Ontario n=1; Quebec n=1); and in 2016, only one XDR-GC was isolated (0.02%, n=1/4,538; British Columbia) (Figure 1).

Trends in resistance patterns

The proportion of *N. gonorrhoeae* that were identified as susceptible to all antimicrobials tested declined significantly (p<0.001) from 67.5% in 2012 to 35.4% in 2016.

In 2012, 2.2% (n=68/3,036) of isolates had decreased susceptibility to cefixime. This proportion has decreased significantly (p<0.001) to 0.3% (n=14/4,538) in 2016 (**Figure 6**). Similarly, decreased ceftriaxone susceptibility was 5.5% (n=168/3,036) in 2012 and decreased significantly (p<0.001) to 1.8% (n=80/4,538) by 2016 (Figure 6).

Figure 6: Decreased susceptibility to cefixime and ceftriaxone and resistance to azithromycin for *Neisseria gonorrhoeae* isolates in Canada, 2012–2016[a]



Abbreviations: mg/L, milligrams per litre; N, total number; ≥, superior or equal to
[a] Percentage based on total number of isolates tested nationally

The proportion of azithromycin resistance increased significantly (p<0.001) from 0.8% (n=25/3,036) in 2012 to 7.2% (n=327/4,538) in 2016 (Figure 6). The modal MICs of isolates resistant to azithromycin decreased from 8 mg/L between 2012 and 2014 to 2 mg/L in 2015 and 2016. The range of the MICs was 2 mg/L to 16 mg/L between 2012 and 2015. In 2016, the range was 2 mg/L to 32 mg/L. There were eight isolates with a MIC of 32 mg/L in 2016. Six of these isolates were MDR-GC, the remaining two were only resistant to azithromycin and erythromycin. The above ranges do not include two isolates with a high level of azithromycin resistance (MIC of azithromycin greater than or equal to 256 mg/L), which were identified in 2012 (n=1) and in 2016 (n=1). Both high-level azithromycin resistant isolates were classified as MDR-GC. In 2016, azithromycin resistance was identified in six provinces across Canada with over 90% (n=306/327) identified in Quebec and Ontario (Quebec, 64.5%; Ontario, 28.1%; British Columbia, 2.1%; Alberta, 3.0%; Nova Scotia, 0.9%; and Saskatchewan, 0.3%).
In 2016, 47.1% (n=2,136/4,538) of isolates were resistant to ciprofloxacin; 31.7% (n=1,439/4,538) of the isolates were resistant to erythromycin; 17.4% (n=791/4,538) were resistant to penicillin; and 53.3% (n=2,419/4,538) were resistant to tetracycline. Most of these isolates were resistant to more than one antimicrobial. Spectinomycin resistance was not detected in any isolates tested in 2016.

Discussion

The proportion of MDR-GC isolates in Canada increased between 2012 and 2016. While the proportion of *N. gonorrhoeae* with decreased susceptibility to cephalosporins has decreased, the proportion of isolates resistant to azithromycin has increased, driving the overall increase in MDR-GC. The XDR-GC are rare in Canada and the proportion identified decreased between 2012 and 2016, due to the decline in isolates with decreased susceptibility to the cephalosporins.

In 2013, Canada's treatment guidelines for uncomplicated gonococcal infection changed from monotherapy with third-generation cephalosporins to combination therapy with ceftriaxone plus azithromycin (6). Once the combination therapy was introduced, a declining trend of decreased cephalosporin susceptibility was identified. The UK, Australia and the (US) have reported similar trends. Combination antimicrobial therapy (ceftriaxone 500 mg IM and azithromycin 1 g orally, in a single dose) was recommended for treatment of uncomplicated gonococcal infections in the UK in 2011 (35). After implementation of the new guidelines, isolates with decreased susceptibility to cefixime declined significantly from 10.8% in 2011 to 5.2% in 2013 (36) and then to 0.6% in 2015 (37). Australia also changed their recommended treatment guidelines (to 500 mg ceftriaxone plus 1 g azithromycin) in 2013 (38). The proportion of isolates with decreased susceptibility to ceftriaxone declined from 4.4% in 2012 (39) to 1.1% in 2017 (40). The recommended therapy for uncomplicated gonococcal infections in the US was updated to ceftriaxone (250 mg IM) combined with azithromycin (1 g orally) in 2012 (41). In the US, decreased susceptibility to cefixime declined from 0.9% in 2012 to 0.3% in 2016 and decreased susceptibility to ceftriaxone remained stable at 0.3% in 2012 and 2016 (42).

While the proportion of decreased susceptibility to cephalosporins has decreased in Canada, the proportion of azithromycin-resistant isolates has increased to 7.2% in 2016 (5), with the majority identified in Quebec and Ontario. Once antimicrobial resistance is established in a region, there is a high risk of these isolates spreading into neighbouring jurisdictions via social networks (43). In 2016, the level of resistance exceeded the 5% level at which the World Health Organization recommends reviewing and modifying national guidelines for treatment of sexually transmitted infections (25). Australia reported similar levels of azithromycin resistance (9.3% in 2017) (44) to Canada; however, the levels in the US (3.6% in 2016) (37) and the UK (4.7% in 2016 [MIC greater or equal to 1 mg/L]) (45) were lower.

The UK and Australia recently reported treatment failures due to high-level XDR-GC with ceftriaxone (MICs=0.5 mg/L) and high-level azithromycin resistance (MIC greater than or equal to 256 mg/L) (24). These strains of XDR-GC threaten the success of the current recommended therapy. With the emerging risk of ceftriaxone resistance and the increasing rate of azithromycin resistance, the *Canadian Guidelines on Sexually Transmitted Infections* has added an alternative combination therapy (gentamicin, 240 mg IM plus azithromycin, 2 g oral) to the list of recommended gonococcal therapies (6).

Strengths and limitations

The strength of this study is that it is a national laboratory-based surveillance system that can identify changing trends in gonococci antimicrobial resistance patterns over time. The limitations of this study include the representativeness of isolates collected in a passive surveillance system, which may be biased towards cultures isolated from specific populations seeking treatment at clinics that provide culture diagnostics. This could lead to considerable missing data concerning affected populations. The epidemiological data are limited and there is a lack of data pertaining to risk factors and demographics. In Canada, cultures were only available for approximately 22% of reported cases for this study period and the remaining cases were diagnosed using NAAT (5); for these cases, antimicrobial susceptibilities were unknown. In addition, the provinces collect cultures according to their own provincial guidelines and perform antimicrobial susceptibility testing using various susceptibility-testing methods.

Next steps

To address the lack of surveillance data in the jurisdictions that have data only from NAAT, the NML developed assays that can be used to predict antimicrobial resistance and sequence type directly from NAAT specimens (46–48). While these assays cannot replace culture-based MIC determinations, they can aid in surveillance by predicting antimicrobial susceptibilities to cephalosporin, ciprofloxacin and azithromycin and, together with molecular typing, can provide an understanding of the types of gonorrhea circulating in a community. This work is not routinely performed but is reserved for remote regions where bacterial culturing is not possible.

To address some of the limitations associated with the national passive laboratory surveillance program, PHAC launched the Enhanced Surveillance of Antimicrobial Resistant Gonorrhea in 2013 (49). Laboratory data, such as antimicrobial susceptibility data and sequence typing, are linked to enhanced epidemiological data, which includes demographic and clinical information, risk behaviours, infection site and prescribed treatment information (49). This enhanced laboratory-epidemiological linked surveillance program is currently being conducted in several provinces with plans to expand to other jurisdictions. These data will improve the understanding of antimicrobial-resistant *N. gonorrhoeae* in Canada and provide better evidence to inform the development of treatment guidelines and public health interventions.

Conclusion

Although rates of MDR-GC increased between 2012 and 2016, XDR-GC in Canada is currently rare. The data presented in this report support efforts to limit the spread of antimicrobial-resistant *N. gonorrhoeae* and prevent the emergence of XDR-GC. In some parts of Canada, azithromycin-resistant GC have exceeded the 5% level at which the World Health Organization recommends reviewing and modifying treatments. Continued surveillance of gonococcal antimicrobial susceptibilities is vital to inform treatment guidelines and mitigate the spread of MDR-GC and XDR-GC.

Authors' statement

IM – Conceptualization, methodology, validation, visualization, writing-original draft, review and editing of final version, supervision, project administration
PS – Investigation, data curation, formal analysis, visualization, writing-original draft sections, review and editing of final version
VA – Resources, methodology, writing-review and editing
BL – Resources, methodology, writing-review and editing
LMNH – Resources, methodology, writing-review and editing
PN – Resources, methodology, writing-review and editing
JM – Resources, methodology, writing-review and editing
PVC – Resources, methodology, writing-review and editing
DH – Resources, methodology, writing-review and editing
RRG – Resources, methodology, writing-review and editing
GZ – Resources, methodology, writing-review and editing
AC – Resources, methodology, writing-review and editing
GG – Resources, methodology, writing-review and editing
KT – Writing-review and editing
MRM – Methodology, writing-review and editing, project administration

Conflict of Interest

None.

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Addressing the rising rates of gonorrhea and drug-resistant gonorrhea: There is no time like the present

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Abstract

Increasing rates of gonococcal (GC) infection and antimicrobial resistant (AMR) GC, are a serious public health concern for Canada and around the world. Previously recommended treatments are ineffective against many of the gonorrhea strains circulating today. The current recommendation for combination therapy is now being threatened by globally emerging and increasingly resistant strains. It is important that coordinated efforts be made now to ensure these new global strains do not become established in Canada. Otherwise, we will be faced with the possibility of persistent GC infection which can lead to pelvic inflammatory disease, infertility and chronic pelvic pain in women; and epididymitis in men. The presence of GC can also increase the risk of HIV acquisition and transmission.

There are a number of reasons why we are facing this public health threat. GC infection is often asymptomatic and it is highly transmissible. People may hesitate to seek testing (or to offer testing). Treatment is complex: recommendations vary by site of infection and risk of resistance. Sexual contact during travel is an important source of imported emerging resistant global strains. The new screening and diagnostic Nucleic Acid Amplification Test (NAAT) is excellent but has decreased the number of cultures being done and therefore our capacity to track AMR-GC.

There are four key actions that clinicians and front-line public health professionals can take to stem the increase in rates of GC and drug resistant GC. First, normalize and increase GC screening based on risk factors and emphasize the need for safer sex practices. NAAT is useful for screening, but culture is still needed for extra-genital sites. Second, conduct pretravel counselling and include a travel history as part of the risk assessment. Third, use culture along with NAAT to establish the diagnosis and follow up for test-of-cure. Finally, refer to the most current *Canadian Guidelines on Sexually Transmitted Infections* or provincial/territorial recommendations on combination therapies for patients and their contacts as recommendations may have changed in response to evolving AMR-GC trends.

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Introduction

Increasing antimicrobial resistance (AMR) in *Neisseria gonorrhoeae*, seen both domestically and internationally, combined with rising rates of gonococcal (GC) infection, are a serious public health concern. Although GC is treatable, global rates continue to rise. The World Health Organization (WHO) estimates that 78 million people are infected with GC annually, as a result of decreased condom use, increased urbanization and travel, poor infection detection rates and inadequate or failed treatment (1).

The Public Health Agency of Canada (PHAC) provides annual national data on GC infection rates (2), laboratory surveillance of AMR-GC (3), and recommendations on the prevention, early detection and treatment of gonorrhea in the *Canadian Guidelines on Sexually Transmitted Infections* (CGSTI) (4). Due to the documented increase in rates of gonorrhea and AMR-GC, PHAC is identifying the need for concerted clinical and public health action.

Rates of gonorrhea have been increasing steadily over the last few years. The number of cases reported in 2016 was more than double the number reported in 2010 (rising from 33.5 to 65.4 per 100,000 population), corresponding to a 95% increase in rates. Males accounted for at least 56% of all cases diagnosed. The most commonly affected age group was 15 to 39 year olds; they comprised 82% of reported cases of gonorrhea, although they represented only 33% of the total population. However, the rates among those aged 40+ have doubled in the past ten years (2).

N. gonorrhoeae now shows resistance to six previously recommended treatment options: sulfonamides, penicillins, earlier generation cephalosporins, tetracyclines, macrolides, and fluoroquinolones (5). The current options for first-line therapy are the third generation extended-spectrum cephalosporins (cefixime, ceftriaxone) and azithromycin. For the purposes of tracking resistance, AMR-GC has been classified as either multidrug-resistant gonococci (MDR-GC) or extensively drug-resistant gonococci (XDR-GC). MDR-GC is defined as a GC strain with decreased susceptibility/resistance to one currently recommended therapy (cephalosporin or azithromycin) plus resistance to at least two other antimicrobials. XDR-GC is defined as a GC strain with decreased susceptibility/resistance to two currently recommended therapies (cephalosporin and azithromycin) plus resistance to at least two other antimicrobials (6,7).

In Canada and globally, isolates are exhibiting decreased susceptibilities to the extended-spectrum cephalosporins and increasing resistance to azithromycin, and treatment failures have been reported (8–11). In this issue, Martin et al. identify that between 2012 and 2016, the proportion of MDR-GC isolates increased from 6.2% to 8.9% and that XDR-GC was rare (0.1% over the same 4-year period) (7). The resistance profile varied by antibiotic. The proportion of isolates with decreased susceptibility to cephalosporins declined between 2012 and 2016 (from 5.9% to 2.0%). During the same period, however, azithromycin resistance increased from 0.8% to 7.2% with some regional variability: the rates were highest in Quebec (18%) and Ontario (5%) (7).

While the low rates of XDR-GC are encouraging, there are new concerns about MDR-GC in Canada. Since the Martin study, two travel related cases were reported with ceftriaxone-resistant strains of GC not previously seen in Canada. The first case was an asymptomatic female whose partner had travelled to China and Thailand (11,12). The second case was a male who had a sexual contact with someone who was visiting from Southeast Asia. Isolates from both cases were genetically liked to *N. gonorrhoeae* strain FC428, first identified in Japan (2015). Both cases were eventually successfully treated; the first with high dose cefixime and azithromycin (11,12) and the second with gentamicin and azithromycin (*Personal communication, Petra Smyczek, Alberta Health Services, July 31, 2018*). This strain has now been identified and characterized in a number of other countries through travel (e.g., Australia, France, Ireland) (11–14). Globally, cases of XDR-GC with High-Level azithromycin (HL-Az) resistance have been reported in the United Kingdom and Australia (15–17); some of these cases were also associated with travel to Southeast Asia.

It is important that efforts be made now to curtail the progression of AMR-GC in general, and to ensure that novel resistant strains (both MDR-GC and XDR-GC) not become established in Canada. Failure to prevent this could add to the already significant morbidity caused by GC infection.

Undiagnosed/untreated GC infection is not benign. In women, it can lead to pelvic inflammatory disease (PID), ectopic pregnancy, chronic pelvic pain and infertility. In men, it can cause epididymitis (pain and swelling of the testicles). The presence of GC can also increase the risk of HIV acquisition and transmission (18–20).

How has this treatable infection become such a public health threat? The objective of this article is to identify how this happened and more importantly, what we can do about it. We make the case that there are four actions that every clinician and front-line public health professional can do to stop the rising GC rates and prevent emerging MDR-GC and XDR-GC from becoming established in Canada.

How did this happen?

There are at least seven factors that have led to this situation.

Gonorrheal infections are often asymptomatic

Women are usually asymptomatic or have only minor symptoms that can easily be ascribed to something else (21–23). Men with urethral gonococcal infection usually have symptoms, but in both genders, rectal and pharyngeal infections are more likely to be asymptomatic (24–26).

Gonorrhea is highly transmissible

Gonococcal infection spreads easily. The estimated transmission rate from a single sexual encounter is 50% to 60% from an infected man to an uninfected woman and 20% from an infected woman to an uninfected man (27). This combination of a highly infectious organism along with a lack of symptoms results in a high rate of onward transmission.

Sexual contact during travel is not uncommon

It is well documented that travel is associated with sexual risk-taking (28–30). Travel is often described as a temporary escape from social expectations in everyday life, contributing to a sense of anonymity and engaging in behaviours that may not be acceptable at home (30–32). Estimated pooled prevalence of travel-related, casual sex among international travellers is approximately 20% to 34% (30,33). Gay, bisexual, or men who have sex with men (gbMSM) are 2–3 times more likely to report a new sexual partner while overseas (34–36) and the proportion of gbMSM having unprotected anal intercourse with a casual partner abroad ranges from 22% to 60% (30).

The recent reports of the novel strain FC428 in travel-related AMR-GC cases in Canada reminds us that certain parts of the world, most particularly Southeast Asia, have seen the emergence of novel resistant strains (MDR and XDR) that pose a risk to Canadians.

People are reticent to seek or offer testing

Unfortunately, there are multiple reasons why people may not seek testing. Individuals tend to underestimate their personal risk. They may perceive that sexually transmitted infections (STIs) are not serious, may be fearful of invasive procedures, or self-conscious about a genital examination. There may be other barriers, such as perceived or anticipated attitudes of health care providers and clinic staff, which can result in individuals feeling judged and discriminated against (37,38). For example, it has been reported that only 49% to 70% of gbMSM have disclosed their sexual orientation to physicians (39,40). Lastly, social barriers exist when individuals fear social condemnation (stigma) with STI testing (37).

Health care providers may not offer testing. Those who don't deal frequently with screening/management of STI may lack knowledge of when and how to test for STI, as well as how to treat a positive result. Discomfort with taking a sexual history and performing genital exams, and a lack of time due to competing medical priorities, have been cited as barriers to STI testing (41–44).

Treatment recommendations can change and are complex

Treatment recommendations keep changing to keep up with the changing resistance profiles. For example, based on rising resistance levels, PHAC changed its first-line treatment recommendations to combination therapy in 2013 (i.e., ceftriaxone/cefixime plus azithromycin). In 2017, PHAC issued an additional alternative treatment recommendation (gentamicin and azithromycin) for GC infections (45). Not all clinicians may be informed of these changing recommendations or they may follow other recommendations.

Treatment recommendations are also complex. Drugs and dosages may differ by the site of the infection or the sexual activity of the person affected. This means that treatment prescribed for an uncomplicated genital infection will not be adequate to treat a pharyngeal infection, which is more difficult to eradicate.

Canada has lost some capacity to track resistant gonorrhea

The use of Nucleic Acid Amplification Test (NAAT) has largely been seen as an advance in GC diagnostics, mainly because of its ease of use (it can be done on urine) and its high sensitivity—up to 100% in some cases. One of the unintended consequences of NAAT is that fewer cultures are being taken as a result, and cultures are currently required for antimicrobial susceptibility testing. In 2016, for example, of the 23,708 cases reported, only about 19% were cultured (46). This means that direct AMR data was only available on approximately one-fifth of GC cases in Canada.

Resistant strains have a competitive advantage over non-resistant strains

MDR and XDR strains of any bacterial infection can spread quickly. Since they are difficult to treat, transmission can continue unabated.

Recommendations for action

In light of the recent development of novel strains resistant to our remaining first-line treatment options, there are four actions that clinicians and front-line public health professionals can do.

1. Normalize and increase screening and promote safer sex practices

There are several ways that health care providers can reduce the hesitations around testing. One key strategy is to normalize it and offer screening for GC—and other sexually transmitted and blood-borne infections (STBBI) with similar routes of transmission—in the course of routine medical care. Using urine NAAT for screening can reduce barriers as it is less invasive for the patient and less time consuming for the clinician.

Be alert for opportunities to have a conversation about STI risks, safer sex practices and the benefits of screening. Perform a risk assessment and offer STI screening to individuals seeking contraceptive advice or to individuals who have a new partner. Although young adults are at the highest risk for STIs, middle aged and older adults may also be at risk and could benefit from screening. Emphasize the need for consistent and correct use of condoms.

The Canadian Public Health Association has developed an excellent resource on best practices when discussing sensitive issues regarding sexual health, substance use and STBBIs to assist providers in the course of assessing risk and/or educating patients (47). This resource may reduce barriers related to discomfort with discussing risk behaviours. A brief risk assessment can be used to quickly identify or rule out major risk factors associated with the increased risk of STIs. Any patient whose current or past history identifies a potential risk factor for STI should be asked to complete a more detailed history.

Screening recommendations

Screening should be offered based on risk. Major risk factors for GC infection include:

- A history of STI (including HIV infection)
- A partner who has been diagnosed with GC
- Sexually active youth less than 25 years of age (due to the high burden of disease in this age group)
- Unprotected sex
- Multiple partners
- gbMSM
- Having a new sex partner in the context of travel

Screening is particularly important during pregnancy, as untreated infection can cause serious illness in the newborn. The Canadian Paediatric Society issued a recommendation against prophylaxis for ophthalmia neonatorum (48). All pregnant women at risk should be screened at the first prenatal visit or at the time of delivery if not previously screened. In serodiscordant couples, the presence of GC chlamydia or other STI in either partner can increase the risk of HIV transmission (18–20).

NAAT and culture in asymptomatic patients

For screening asymptomatic males, first-void urine for NAAT is the test of choice (49). For screening asymptomatic females, vaginal swabs are preferred and may also be self-collected. Cervical swabs for NAATs can be taken. Urine-based NAAT is ideal when a pelvic examination is not indicated or is refused.

Depending on the history and the clinical situation, it may be appropriate to take samples from multiple (i.e., all exposed) anatomical sites. Culture remains the preferred test for screening of extra-genital (pharyngeal and rectal) infections (a validated NAAT may be used if culture is not available). As pharyngeal infections are usually asymptomatic, using culture to screen those with a history of performing oral sex is extremely important.

2. Conduct pretravel counselling and take a travel history

Health care providers need to counsel travellers prior to travel on the need for safer sex practices. Depending on the destination, it may be appropriate to discuss specifically the risk of AMR-GC infection.

When an individual presents with symptoms or a possible exposure to an STI, the assessment should include a travel history. If the travel risk assessment identifies unprotected sexual exposure during travel there should be a heightened index of suspicion for potential AMR-GC infection, and more specifically, a resistant strain not currently circulating in Canada.

3. Increase diagnosis and follow-up with a test-of-cure

Cultures are important for the diagnosis of symptomatic patients, and critical for gaining information on antimicrobial resistance testing. However, NAAT is important too, as it is the most sensitive diagnostic test. When a patient has signs and/or symptoms consistent with GC, the use of culture together with NAAT is extremely useful. This permits antimicrobial susceptibility testing and identification of AMR strains, while the use of highly sensitive NAAT reduces the number of missed diagnoses.

Samples should be taken from all exposed sites. If symptomatic patients are given empiric therapy (i.e., before test results are available), specimens should be obtained prior to treatment. Due to high rates of concomitant infection, specimens should be taken for the diagnosis of both GC and chlamydial infections (50).

Test for urogenital gonorrhea

In symptomatic men with urogenital infections, a urethral swab for gram stain and culture should be obtained when possible. When culture testing is not available, urine NAAT can be used (51). In symptomatic women, collect a cervical or vaginal swab for culture and for NAAT. The use of culture is important and is strongly recommended, especially under certain circumstances (e.g., to evaluate pelvic inflammatory disease and in pregnancy). Vaginal swabs or urine are suitable samples for NAAT. In patients with urethral symptoms, a urethral swab for culture can also be used.

Test for extra-genital gonorrhea

For sexually active individuals with extra-genital signs and symptoms or with a history of performing oral sex or having receptive anal intercourse, collect pharyngeal and rectal specimens for testing. Culture remains the preferred testing method for diagnosis of extra-genital infections, which are often asymptomatic. If culture is not available, check whether your laboratory has done an in-house laboratory validation on clinical specimens (i.e., pharyngeal and rectal) other than the manufacturer's recommended specimen type (i.e., urine). If it has, this "validated" NAAT may be used for extra-genital specimens.

Follow-up with a test-of-cure

Take follow-up cultures for test-of-cure from all positive sites 3–7 days after the completion of treatment. If NAAT is the only option for test-of-cure, take the 2–3 weeks after completion of treatment to avoid false-positive results.

Tests-of-cure are particularly important for:

- Pharyngeal infections
- Pregnant women
- High risk of AMR-GC (i.e. diagnosed in partner or following travel and sexual contact in an area with a high burden of AMR-GC)
- Alternative treatment regimens when ceftriaxone was the first-line treatment but intravenous therapy was not possible
- Persistent signs/symptoms

Repeat screening six months post-treatment is recommended due to the risk of reinfection.

4. Provide up-to-date combination therapy to patients and their contacts

Treat all patients with GC with combination therapy (52). The use of two antimicrobials with different mechanisms of action is thought to improve treatment efficacy as well as to prevent or potentially delay the emergence and spread of AMR-GC. In order to prevent development of AMR, monotherapy with azithromycin, 2 grams should be avoided unless there is no other option. Prompt and appropriate treatment of infected individuals, and all sexual partners from the preceding 60 days, is essential to prevent the spread of infection. The local public health professionals can assist with contact tracing and notification as needed.

All individuals should be treated according to current recommendations (45). These recommendations are also available and accessible through the CGSTI mobile application. This application provides quick and convenient access to up-to-date Canadian guidelines on the diagnosis and management of STI. It is available for free for Apple™ and Android™ devices and can be accessed via the CGSTI website (4).

Treatment recommendations

Recommended combination therapy varies depending on site of infection and probability of resistance. In particular, the CGSTI differentiates between treatment options for uncomplicated anogenital gonococcal infections, and the treatment of pharyngeal infections (in all adults) as well as infections among gbMSM.

Check the CGSTI or STI guidance from local or provincial/territorial (P/T) public health for details on treatment recommendations (4). Local or P/T guidance should be followed when treatment choices have been informed by local or P/T resistance data.

When cephalosporins are contraindicated because of allergy or resistance, the CGSTI recommend treatment with alternative combination therapy regimens that include gentamicin (4).

If persistent infection is suspected following treatment, both culture and antimicrobial susceptibility testing should be performed to verify treatment failure and assess effective and appropriate treatment options. Consultation with an infectious disease specialist is warranted.

These four key recommendations for action are summarized in **Table 1**.

Table 1: Four key recommendations needed to preserve options for remaining first-line treatment of antimicrobial resistant gonorrhea

Recommendations	Details
Normalize and increase screening and promote safer sex practices	• To reduce barriers and associated stigma, look for opportunities during routine medical care to have a conversation about STI risks, safer sex practices and the benefits of screening • Samples should be taken from all sites of exposure, to increase diagnosis and ensure appropriate treatment is provided
Conduct pretravel counselling Include a travel history in your risk assessment	• Counsel travellers on the importance of safer sex practices while travelling; depending on the destination, it may be appropriate to discuss the risk of AMR-GC infection specifically • If there is a history of unprotected sexual exposure during travel, maintain a heightened index of suspicion for potential AMR-GC infection, and more specifically, a globally emerging resistant strain not currently circulating in Canada
Increase the use of cultures for diagnosis and test-of-cure	• NAAT is convenient and highly sensitive and can increase the diagnosis of GC. Culture provides information on antimicrobial susceptibilities prior to treatment and is critical for improved public health monitoring of antimicrobial resistance patterns and trends • When signs and/or symptoms are consistent with gonococcal infection, the use of culture along with NAAT is extremely important
Provide up-to-date combination therapy for patients and their contacts	• Due to increasing antimicrobial resistance, combination therapy is the standard of care choice of combination therapy should be guided by infection site and patient history. AMR resistance patterns may show regional variation • Consult the CGSTI or your jurisdiction's STI guidance for details on treatment recommendations • Treatment of all sexual contacts from the previous 60 days is essential. Local public health professionals can assist with contact tracing and notification as needed

Abbreviations: AMR, antimicrobial resistance; CGSTI, Canadian Guidelines on Sexually Transmitted Infections (4); GC, gonococcal; NAAT, nucleic acid amplification testing; STI, sexually transmitted infection

Discussion

Rates of GC and AMR-CG infections are increasing, both domestically and internationally, and represent a serious public health concern. Clinicians and front-line public health professionals are well placed to proactively screen and treat patients testing positive for GC or AMR-GC, and counsel all those at risk, on the risks of STIs and travel. Cultures are needed for diagnosis when possible, and to assess treatment effectiveness, to prevent ongoing transmission and allow for effective monitoring of AMR.

New national initiatives

In addition to the efforts of front-line professionals, PHAC has put in place several initiatives to further improve the understanding and current levels and trends of AMR-GC infection in Canada and to provide better evidence to inform the development of treatment guidelines and public health interventions.

In 2013, the Enhanced Surveillance of Antimicrobial Resistant Gonorrhea was launched in several jurisdictions. This enhanced laboratory-epidemiological linked surveillance program collects information on demographics and clinical characteristics, risk behaviours, infection site(s), antimicrobial resistance and susceptibility, sequence typing and prescribed treatment information (53). Treatment data collected by this program in 2016 indicated that the majority of cases were prescribed either the preferred or alternative therapies as proposed by the CGSTI (4).

To support remote regions that cannot culture the GC isolates, the National Microbiology Laboratory (NML) has developed innovative technologies to detect and predict AMR directly from NAAT specimens (54–56). While it is important to note that these assays cannot replace culture-based determination of the minimum inhibitory concentration (MIC), they can still aid in surveillance by predicting antimicrobial susceptibilities of cephalosporin, ciprofloxacin and azithromycin and, together with molecular typing, can provide an understanding of the types of gonorrhea circulating within a community.

Finally, to support the monitoring of global patterns of AMR-GC, PHAC is engaged in international collaboration. National AMR surveillance data is submitted to the WHO Global STI Surveillance report and the Global Antimicrobial Resistance Surveillance System (GLASS). In an effort to standardize the characterization of gonococcal antimicrobial resistance genes, PHAC, in collaboration with researchers from Centers of Disease Control and Prevention (CDC), United Kingdom, Australia and Sweden, developed NG-STAR (*Neisseria gonorrhoeae* Sequence Typing for Antimicrobial Resistance) an on-line sequence based molecular antimicrobial resistance typing scheme for tracking the global dissemination of *N. gonorrhoeae* strains (57).

Conclusion

Collaborative efforts between clinicians and public health professionals at local, provincial/territorial and federal levels are needed to effectively prevent, identify, treat and monitor GC and AMR-GC infections in Canada. There is no time like the present to hone our collective efforts to prevent emerging MDR-GC and XDR-GC strains from taking hold in Canada.

Authors' statement

MB – Conceptualization, methodology, writing-original draft, review and editing, project administration
MGR – Conceptualization, methodology, writing-original draft, review and editing
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Conflict of Interest

None.

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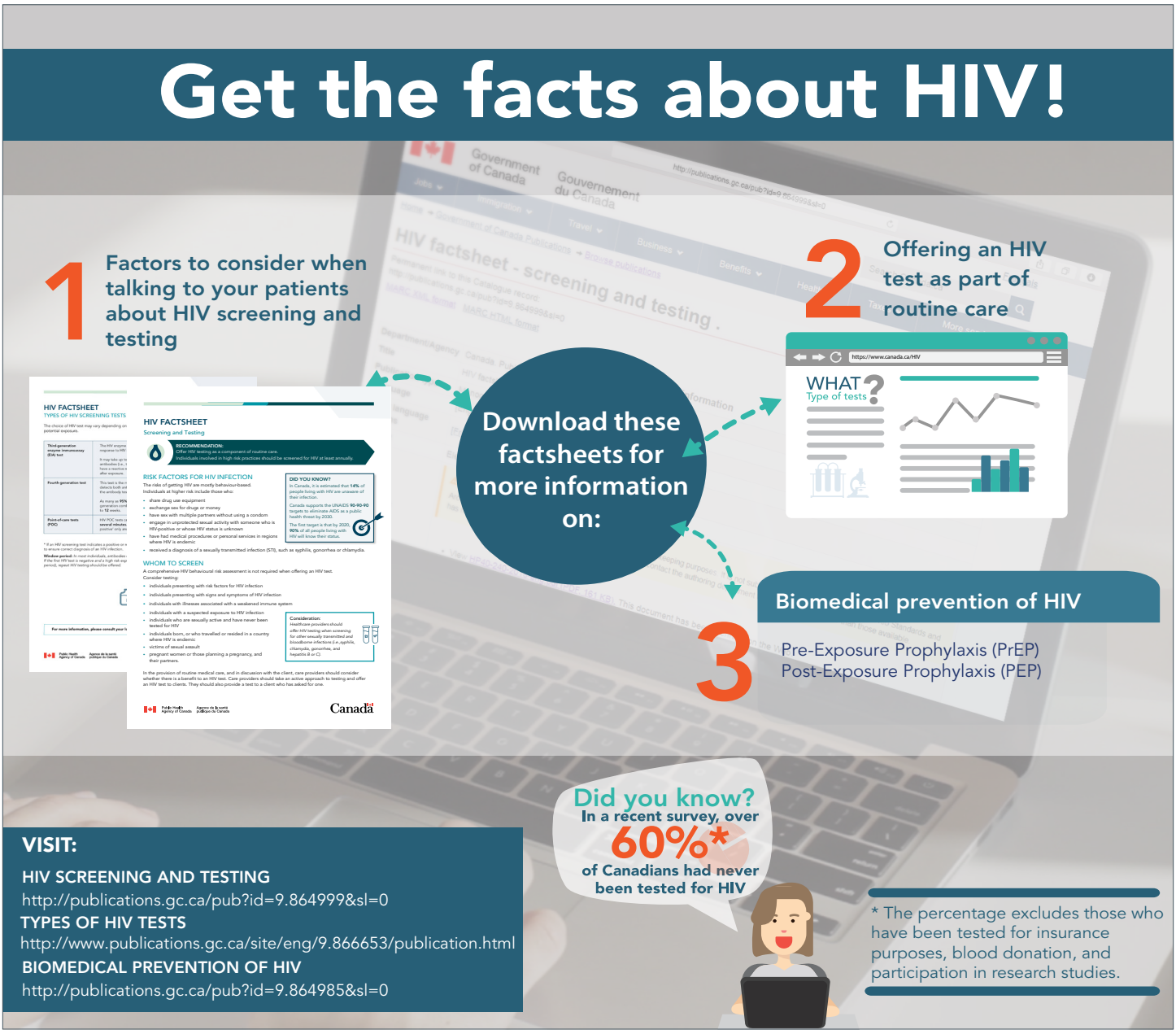

COMMENTARY

The need for integrated public health surveillance to address sexually transmitted and blood-borne syndemics

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Abstract

A national approach to addressing sexually transmitted and blood-borne infections (STBBIs) was recently articulated in the Public Health Agency of Canada's new *A Pan-Canadian Framework for Action: Reducing the health impact of sexually transmitted and blood-borne infections in Canada by 2030*. This Framework promotes an integrated approach, with a focus on the key populations that are affected by overlapping epidemics (i.e., syndemics). We advance the idea that integrating surveillance would be helpful in characterizing and understanding the populations, locations, risk behaviours and other drivers that contribute to STBBI syndemics. The creation of matched or linked data systems that would allow routine reporting of integrated data is challenged by the technical barriers of integrating data silos as well as by the privacy and ethical considerations of merging sensitive individual-level data. Lessons can be learned from jurisdictions where an improved understanding of syndemics, through integrated STBBI surveillance, has led to more efficient and effective operational, program and policy decisions. Emerging enablers include the development of data standards and guidelines, investment in resources to overcome technical challenges and community engagement to support the ethical and non-stigmatizing use of integrated data. The Framework's call to action offers an opportunity for national discussion on priorities and resources needed to advance STBBI syndemic surveillance for local, regional and national reporting in Canada.

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Keywords: *Neisseria gonorrhoeae*, *N. gonorrhoeae* multidrug resistant, antimicrobial resistance, laboratory surveillance, STI, STBBI, sexually transmitted infections, sexually transmitted and blood-borne infections, gonorrhea, gonococcal infection

Introduction

We applaud the Public Health Agency's new document, *A Pan-Canadian Framework for Action: Reducing the health impact of sexually transmitted and blood-borne infections in Canada by 2030*, as a roadmap for federal, provincial/territorial and local public health jurisdictions to consider in their efforts to reduce the health impacts of sexually transmitted and blood-borne infections (STBBIs) in Canada (1). One of the Framework's guiding principles is to move beyond programs and interventions targeted towards single infections by utilizing integrated approaches designed to "address the complexity and interrelated nature of risk factors and transmission routes for STBBIs"—that is, a syndemics approach.

Merrill Singer, a noted medical anthropologist, defined syndemics as "two or more health issues [that] interact synergistically to contribute to increased health burden for individuals or communities" (2). Singer used the interaction of human immunodeficiency virus (HIV) and tuberculosis (TB) co-infections to typify the adverse interactions between two diseases (i.e., the more rapid progression of symptoms and illness occurring from concurrent infections versus single infections of either), and the common conditions of health inequity (e.g., poverty and marginalization) that contribute to their clustering and spread (3). In a more recent example, a study from British Columbia characterized the epidemic of syphilis among gay, bisexual and other men who have sex with men, and its associations with substance use, mental health and co-infection with HIV. Additionally, the association was higher for those reporting multiple co-morbid conditions (4). Applying a "syndemic lens" enhances efforts to measure and address known risk factors for single diseases by characterizing their multiplicative effects and impacts across diseases.

Syndemics also necessitates community engagement and ethical frameworks to ensure that data are presented in such a way as to prevent further stigmatizing of vulnerable groups that may be associated with an excess burden of illness.

The goals of the Framework would be well supported by public health surveillance that uses an integrated approach to help inform and prioritize public health action. Currently, most public health surveillance systems focus on single diseases. They are not designed to report on multiple and interacting causes of STBBIs, such as concurrent and previous STBBIs, common risk factors across infections, social determinants of health and environmental factors (e.g., availability of testing/treatment locations). Understanding the synergistic impacts of these causes of disease would enable the development and prioritization of strategic operational, program and policy decisions (5). For example, monitoring the timing and prevalence of sexually transmitted co-infections, along with factors impacting testing and treatment, could be used in the planning and evaluation of HIV preexposure prophylaxis programs, particularly as these programs are being scaled up across Canada (6).

Although an integrated STBBI surveillance system is a laudable goal, creating the necessary data infrastructure and supporting policies is a major undertaking. The objective of this article is to highlight examples of jurisdictions currently engaged in this work and to explore the challenges and potential enablers to adopting integrated STBBI surveillance systems.

Examples of surveillance integration

Public health organizations around the world are engaged in a range of activities to integrate and report on STBBI syndemics. An example of this activity is AtlasPlus: an interactive website, hosted by the United States' Centers for Disease Control and Prevention (CDC), designed to visualize the rates of STBBIs and TB infections and the measures of social determinants of health at the state level (7). AtlasPlus enables side-by-side comparisons of combinations of metrics for two infections, along with area-based social determinants, but does not include linked or matched data. There are two significant advantages of this tool: single-disease data can be refreshed independently and in a timely manner; and any number of measures of social determinants or other drivers can be overlaid as long as they are available at similar geographic levels. While interpretations are limited to ecological associations, this tool stimulates hypothesis-generation and further exploration.

The CDC has also supported the integration of surveillance for HIV, sexually transmitted infections (STIs), viral hepatitis and TB at both the state and local levels through two funding initiatives: the Outcome Assessment through Systems of Integrated Surveillance (OASIS) initiated in 1998; and the Program Collaboration and Service Integration initiated in 2007 (8,9). These initiatives provided funding for database development and established communities of practice to advance capacity-building for the analysis and use of integrated data. The New York City Health Department created a 10-year matched dataset of patients with viral hepatitis, TB, STIs and HIV, complete with vital statistics death data. With this cohort, they described the overlapping risk factors across infections and higher than expected mortality associated with multiple infections (10). Subsequently, non-infectious disease outcomes, such as the prevalence of diabetes, are now being matched to this dataset to examine their associations with STBBIs and TB (11).

Another example is from Los Angeles County Public Health, where neighbourhood maps were overlaid with information on HIV/STI co-infection clusters, locations of existing testing sites and income measures to identify high burden service planning areas (12). Los Angeles County Public Health have gone on to develop health district profile maps, using matched data, that allow for reporting of sociodemographics, behaviours, co-infections and recurrent infections at the level of individual patients. Demographic subgroup and infection characteristic data are helpful for targeting of programs. Health districts are also ranked by these indicators to support the geographic prioritization of resources for HIV and STI prevention and treatment (13).

Jurisdictions in Canada have similarly leveraged existing linked databases to assess the impact of co-infections in individuals. Alberta's *2013 Annual Report on STI and HIV* included a matched analysis of the prevalence and timing of STI co-infection (before, same time or after HIV infection) in individuals diagnosed with HIV between 2005 and 2013 (14). These results demonstrated a change over time: before 2007, the majority of individuals were diagnosed with an STI before or at the same time as their HIV diagnosis, whereas in 2013, individuals were twice as likely to have been diagnosed with an STI after their HIV diagnosis. While the co-occurrence of HIV and STIs is well documented, this kind of surveillance data helped identify a local change in trends over time. This type of information can be used to guide STBBI programs to adapt their testing and prevention strategies for individuals who are at risk of, or who have been diagnosed with HIV.

An example of a jurisdiction moving from studies of one-time cohorts towards ongoing, integrated surveillance is the British Columbia Hepatitis Testers Cohort (BC-HTC). This is a population-based research cohort, using provincial STBBI surveillance and public health laboratory data that is linked to the BC Cancer Registry and BC's prescription dispensing and healthcare utilization databases. This cohort has been used to monitor a cascade of care for hepatitis C within key populations, including people living with HIV and people who inject drugs (15). Because this cohort is updated regularly, ongoing cohort analyses are expected to help inform the development and evaluation of programs and policies addressing this syndemic (16). As well, the matching algorithms developed for the BC-HTC are now being applied to improve routine surveillance from the BC Centre for Disease Control data warehouse that facilitates STBBI reporting for BC (17).

Challenges and enablers

For both BC and New York City, many years were required to create the infrastructure needed to analyze key populations. In light of this, other jurisdictions that may not have begun this process may wonder whether the questions answered by integrated STBBI data are worth the efforts, compared with what can be learned when traditional epidemiological methods are applied to single diseases. Even if there is support for integrated surveillance, there may still be debate on:

- What are the most important questions that need to be answered by integrated surveillance?
- What is the most appropriate level (local, regional, national) to address those questions?

Jurisdictions that already have the infrastructure in place may now face the challenges of working with various stakeholders to identify priorities for outputs, when so many analyses are now possible. Here, resource limitations may drive the prioritization of surveillance activities and, simultaneously, integrated surveillance can help guide the appropriate allocation of resources.

There are a number of challenges to integrated surveillance. In a 2007 survey of CDC-funded STI programs that examined the extent of surveillance integration in these programs (18), barriers to increased integration were first identified and included the following: restrictive data policies, particularly for HIV data that are siloed from other systems; incompatible databases, which complicated the linking of data; lack of time and technical expertise in linking and managing data systems; and lack of financial resourcing. Subsequent to this survey, the CDC published guidelines for STBBI data security and confidentiality that set out data standards for the technical and privacy considerations of collating STBBI data at the local, state and national levels (19). They also set out program standards for CDC-funded public health organizations, based on 10 guiding principles for data collection, storage, sharing and use to ensure security and confidentiality and 32 standards addressing program policies and responsibilities, data collection and use, data sharing and release, physical security and electronic data security.

In addition to overcoming the technical barriers to integrated surveillance, local-level engagement with communities is critical to ensuring that information from such integration does not increase stigmatization of key populations. Advancements in STBBI testing, particularly phylogenetic analyses, has not only raised new opportunities for assessing syndemics but also new ethical and privacy challenges as increased granularity in transmission dynamics may increase the potential for stigmatizing individuals and specific groups (20). One approach to address these challenges is the Ontario HIV Epidemiology and Surveillance Initiative's "Champions Committee", which is comprised of various community members and persons with specific, relevant life experiences; these committees review all the Initiative's HIV surveillance products (21).

Discussion

The document, *A Pan-Canadian STBBI Framework for Action*, calls for surveillance that supports integrated approaches to key populations affected by STBBI syndemics. To achieve these goals, it would be useful to characterize and monitor populations affected by STBBI co-infections and the various factors associated with these infections. While there are challenges and important ethical and privacy considerations for integrating these STBBI data, there are examples from leading jurisdictions, including some from within Canada, that demonstrate both that these challenges can be overcome and the benefits of doing so.

To realize the benefits of integration, organizations involved in STBBI surveillance will have to contend with the unique challenges of their information systems and their supporting data management and dissemination practices. These challenges can be addressed through funding initiatives, communities of practice addressing technical barriers, the development of white papers on data standards, and the establishment of frameworks for the ethical use of linked data.

Conclusion

There is an urgent need to address the growing burden of STBBIs in Canada, and the recent Framework has created an agreed-upon national approach to do so. Ultimately, innovation, investment and collaboration will be needed to facilitate integration of STBBI surveillance to support the goals of this Framework.

Authors' statement

MM – Conceptualization, writing–original draft, review and editing
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Conflict of interest

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Tuberculosis in Canada: 2017

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Abstract

Background: Tuberculosis (TB) is a major global health problem that affected an estimated 10 million people worldwide in 2017. The Public Health Agency of Canada monitors active TB disease through a national surveillance system, which is a collaborative effort with the provinces and territories.

Objective: To present an epidemiological summary of active TB cases reported in 2017. Results are discussed in the context of the previous year's data. Treatment outcomes for cases diagnosed in 2016 are also presented.

Methods: The Canadian Tuberculosis Reporting System is a case-based surveillance system that maintains non-nominal data on people diagnosed with active TB disease in Canada. Data are collected annually from the provinces and territories, analyzed by the Public Health Agency of Canada and validated by each province and territory.

Results: There were 1,796 cases of active TB reported in Canada in 2017 compared with 1,750 cases in 2016, representing a 2.6% increase. There was a corresponding increase in the incidence rate from 4.8 to 4.9 per 100,000 population. Foreign born individuals continued to make up the majority of cases (71.8%) and the incidence rate remained highest among Canadian born Indigenous people (21.5 per 100,000 population), in particular, among the Inuit population (205.8 per 100,000 population). Consistent with the previous decade, TB incidence rates in 2017 continued to be higher among males (5.5 per 100,000) compared with females (4.3 per 100,000), and the majority of cases (45.6%) were between the ages of 15 and 44 years. The incidence rate was highest among adults over 75 years of age (13.8 cases per 100,000 for males and 7.2 for females). Of the TB cases diagnosed in 2016 where outcomes were reported, 80.4% were treated successfully.

Conclusion: Although the incidence rate of TB in Canada in 2017 remained low in the global context and has been relatively stable over the last decade, both the case count and rate have been gradually increasing since 2014. Indigenous and foreign born Canadians continued to be disproportionately represented among TB cases. Canadian TB surveillance data are an important source of information for monitoring progress and informing public health action related to reducing the burden of TB in Canada, with the ultimate goal of TB elimination.

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Introduction

Globally, tuberculosis (TB) is one of the most common infectious diseases and is among the leading causes of death. The World Health Organization (WHO) estimated that there were 10 million new TB cases in the world in 2017 (1). As part of *The End TB Strategy*, the WHO has outlined in *Towards TB Elimination: An Action Framework for Low-Incidence Countries* (i.e., those countries with an incidence rate of 10 TB cases per 100,000 population or fewer), guidance on how to further reduce TB rates to elimination levels (defined as 0.1 cases per 100,000 population) by 2035 (2).

While Canada is a low TB incidence country, TB incidence rates are consistently higher than the low incidence cut-off in certain subpopulations in the country: namely, foreign born and Indigenous Canadians (3). A high level of TB activity in Canada's north has been observed for many years, especially among the Inuit (3,4). Tuberculosis among foreign born Canadians also represents a large burden of illness in Canada (3). Statistics Canada has projected high growth rates in these two populations in Canada when compared with the population of Canada as a whole (5,6), so it is especially important to diagnose and treat TB, both to address the impact of active TB disease on the affected individual and to prevent any further spread.

In Canada, national surveillance of new and re-treatment cases of active TB is conducted in partnership with all provinces and territories by the Public Health Agency of Canada (PHAC). The primary objective of the Canadian Tuberculosis Reporting System (CTBRS), Canada's national case based surveillance system, is to monitor and report on the number of cases and on the rates of active TB in Canada. Annual reporting of TB across the country is important to better understand the epidemiology of TB in Canada over time, to inform public health action and to monitor Canada's progress toward reducing the incidence of TB in Canada, with the ultimate goal of TB elimination (7).

The objective of this report is to provide a descriptive overview of TB cases in Canada in 2017 by age, sex, origin, province/territory and diagnostic classification in the context of previous years' data. Treatment outcomes for TB cases that were reported to the CTBRS in 2016 are also summarized.

Methods

The CTBRS maintains non-nominal data on people diagnosed with active TB disease in Canada. Details on the CTBRS's methods, including data collection processes, data management, data quality control and analysis, and the classification and categorization of population subgroups have been described in detail elsewhere (8). In short, provincial and territorial public health authorities voluntarily submit data on all new and re-treatment cases of active TB disease that meet the Canadian case definition for national surveillance (8). Treatment outcome data are submitted between 12 and 18 months following the submission of the initial case report. If treatment is ongoing at the time of data submission to PHAC, the reporting jurisdiction submits an interim report followed by subsequent annual updates until the case file is closed. Updated data from previous years received after the initial submission is reflected in the most current report.

Active TB is classified as either respiratory or non-respiratory. Respiratory TB includes pulmonary TB, TB of the pleura and TB of the intrathoracic or mediastinal lymph nodes, larynx, nasopharynx, nose and sinuses (9). Primary disease is characterized by pleural effusion due to recent (i.e., within the preceding 24 months) infection with *Mycobacterium tuberculosis*. Non-respiratory TB refers to all other disease sites.

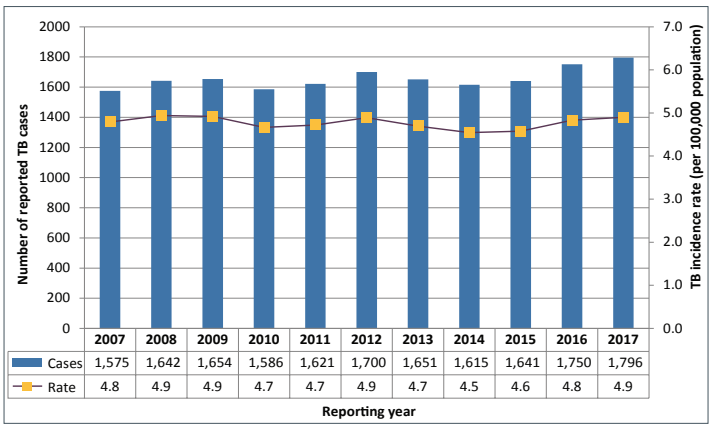
Incidence rates in this report were calculated as cases per 100,000 population. Population data used to calculate these rates came from multiple sources. Canadian population data were based on midyear estimates of the Canadian population from Statistics Canada (*unpublished data*). The foreign born population data were based on the 2016 Canadian Census (10). Estimates of the population of Indigenous groups for 2017, namely First Nations, Métis and Inuit, came from the National Household Survey (11). For First Nations persons with status on and off-reserve, population data came from Crown-Indigenous Relations and Northern Affairs Canada's Indian Registration System as of December 31, 2017 (*unpublished data*).

Original data were maintained according to PHAC's *Directive for the Collection, Use and Dissemination of Information Relating to Public Health*. Data were cleaned and analyzed using SAS™ Enterprise Guide and Microsoft™ Excel 2010. Descriptive findings are presented here. No statistical procedures were used for comparative analyses, nor were any statistical techniques applied to account for missing data. Note that in 2017, British Columbia did not submit information on Indigenous status and, therefore, cases from British Columbia were identified only as either Canadian born or foreign born. Supplementary data tables are available upon request (see **Appendix** for Table list).

Results

There were 1,796 cases of active TB reported in Canada in 2017, compared with 1,750 cases in 2016, representing a 2.6% increase. There was a corresponding increase in the incidence rate from 4.8 to 4.9 per 100,000 population. Of all reported cases in 2017, 92.2% were new cases of active TB and 5.3% were re-treatment cases (i.e., reported having had at least one previous episode of TB). History of previous TB infection was unknown for 2.5% of reported cases. Both the number of cases and the rate of TB in Canada have increased slightly since 2014, when the incidence rate was 4.5 cases per 100,000; however, across the 11 year period, from 2007, the rate increased only slightly (from 4.8 cases per 100,000). The number of TB cases has fluctuated to some extent since 2007, but the absolute number of reported cases in 2017 (1,796 cases) has risen compared with 2007 (1,575 cases) **(Figure 1)**.

Figure 1: Number of reported tuberculosis cases and incidence rates by year, Canada, 2007–2017



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Cases	1,575	1,642	1,654	1,586	1,621	1,700	1,651	1,615	1,641	1,750	1,796
Rate	4.8	4.9	4.9	4.7	4.7	4.9	4.7	4.5	4.6	4.8	4.9

Abbreviation: TB, tuberculosis

Tuberculosis cases by geography

Across Canada, incidence rates of TB varied widely by province/territory in 2017 **(Table 1)**. There were no cases of TB reported in Prince Edward Island. Incidence rates of TB were below the national rate of 4.9 per 100,000 population in Newfoundland and Labrador (2.5), Nova Scotia (0.9), New Brunswick (1.1), Quebec (2.6) and Ontario (4.8), but were slightly higher than the national rate in British Columbia (5.3), Alberta (5.3) and the Northwest Territories (6.7). The highest TB incidence rates were in Saskatchewan (8.1), Manitoba (14.0), Yukon (20.8) and Nunavut (265.8). The majority of cases (64.4%) were concentrated in Ontario (37.6%), British Columbia (14.1%) and Alberta (12.6%). While most provinces and territories reported little change from 2016, in Nunavut the number of cases nearly doubled from 2016 to 2017, and the corresponding incidence rate increased from 145.6 to 265.8 per 100,000 population (Table 1).

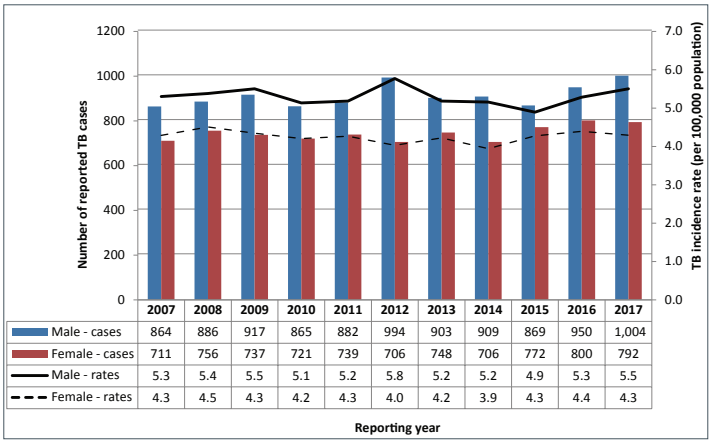
Table 1: Number of reported tuberculosis cases and incidence rates per 100,000 population by province and territory, in Canada, 2016–2017

Province	2016		2017	
	Cases	Rate	Cases	Rate
Newfoundland and Labrador	25	4.7	13	2.5
Prince Edward Island	4	2.7	0	0.0
Nova Scotia	3	0.3	9	0.9
New Brunswick	12	1.6	8	1.1
Quebec	252	3.0	217	2.6
Ontario	641	4.6	676	4.8
Manitoba	201	15.2	187	14.0
Saskatchewan	91	7.9	94	8.1
Alberta	238	5.6	227	5.3
British Columbia	225	4.7	253	5.3
Yukon	1	2.7	8	20.8
Northwest Territories	3	6.7	3	6.7
Nunavut	54	145.6	101	265.8
Total for Canada	1,750	4.8	1,796	4.9

Tuberculosis cases by sex and age

Of the 1,796 reported cases of TB in 2017, 792 (44.1%) were female and 1,004 (55.9%) were male, corresponding to an incidence rate of 4.3 among females and 5.5 among males per 100,000 population. Since 2007, males have consistently accounted for a higher proportion of cases of TB, and correspondingly higher incidence rates (**Figure 2**).

Figure 2: Number of reported cases of tuberculosis and incidence rates by sex and year, Canada, 2007–2017

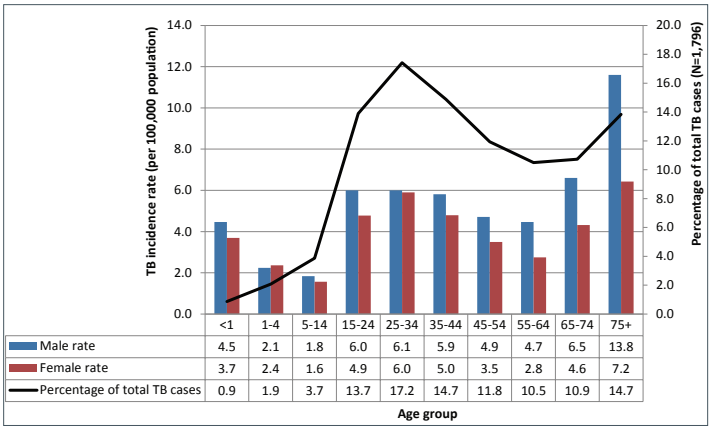


	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Male - cases	864	886	917	865	882	994	903	909	869	950	1,004
Female - cases	711	756	737	721	739	706	748	706	772	800	792
Male - rates	5.3	5.4	5.5	5.1	5.2	5.8	5.2	5.2	4.9	5.3	5.5
Female - rates	4.3	4.5	4.3	4.2	4.3	4.0	4.2	3.9	4.3	4.4	4.3

Abbreviation: TB, tuberculosis

Among cases 44 years of age and younger, TB incidence rates among male and female cases were similar; however, after age 44 years, the incidence rate gap between male and female cases begins to widen. In adults aged 75 years and older, the TB incidence rate for male cases was almost twice that of females (13.8 versus 7.2 cases per 100,000) (**Figure 3**).

Figure 3: Tuberculosis incidence rates by sex and age group and percentage of tuberculosis cases by age group, Canada, 2017



	<1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75+
Male rate	4.5	2.1	1.8	6.0	6.1	5.9	4.9	4.7	6.5	13.8
Female rate	3.7	2.4	1.6	4.9	6.0	5.0	3.5	2.8	4.6	7.2
Percentage of total TB cases	0.9	1.9	3.7	13.7	17.2	14.7	11.8	10.5	10.9	14.7

Abbreviations: N, total number; TB, tuberculosis

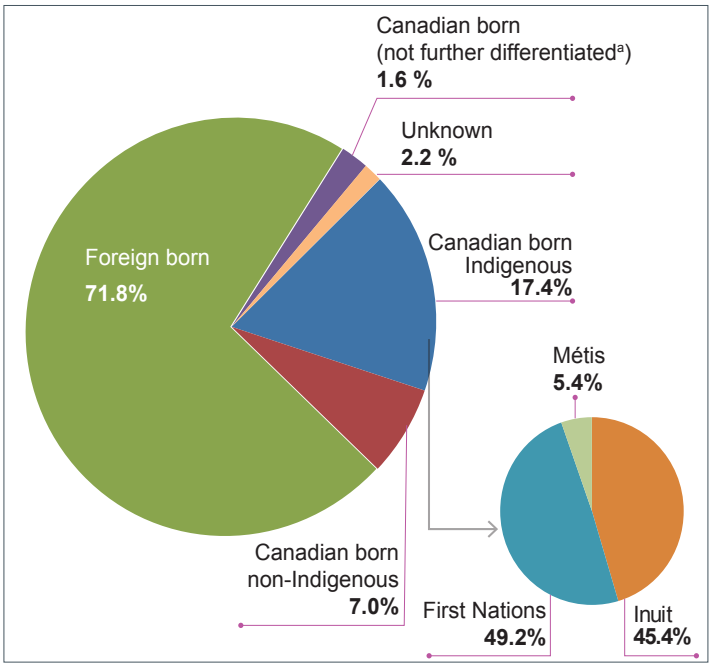
The highest TB incidence rate was among those aged 75 years and older (10.0 cases per 100,000), followed by those aged 25–34 years (6.0 per 100,000). The lowest incidence rate was among those aged 5–14 years (1.7 per 100,000). The incidence rate among children younger than one year of age increased

to 4.1 cases per 100,000 in 2017 from 2.1 per 100,000 in 2016. The largest number of TB cases was in the 25–34 year age group (n=309; 17.2% of total cases) (Figure 3). Children constituted a small proportion of total TB cases in 2017, with infants younger than one year of age accounting for 0.9% of TB cases and children aged one to 14 years accounting for 5.6% of total cases. Trends among TB cases by age have changed little over the past 10 years (3).

Tuberculosis cases by origin

The majority of TB cases reported in Canada in 2017 were foreign born (n=1,290; 71.8%), followed by Canadian born Indigenous cases (n=313; 17.4%) and Canadian born non-Indigenous cases (n=125; 7.0%) (**Figure 4**). An additional 1.6% of cases (n=28) were reported as Canadian born without any further origin breakdown reported, and origin was unknown for a further 2.2% of cases (n=40) (Figure 4).

Figure 4: Distribution of tuberculosis cases by origin, Canada, 2017



[a] Cases in this group could not be further differentiated into Indigenous or non-Indigenous

Indigenous tuberculosis cases

In Canada in 2017, there were 313 cases of TB reported among Canadian born Indigenous persons, resulting in an incidence rate of 21.5 cases per 100,000 population, a slight decrease from 2016, when the rate was 23.3 cases per 100,000 population (**Table 2**). Of these Indigenous cases, 49.2% (n=154) were First Nations, 45.4% were Inuit (n=142) and 5.4% (n=17) were Métis (Figure 4). Among Métis, the incidence rate of TB was 3.5 cases per 100,000 population, which is lower than the overall Canadian rate (4.9 per 100,000) but higher than the Canadian born non-Indigenous rate (0.5 per 100,000). This rate has generally decreased over time, from 7.5 in 2007 to 2.1 cases per 100,000 in 2016, with a slight rise in 2017 (Table 2). Among First Nations persons, the TB incidence rate in 2017 was 17.1 cases per 100,000 population, which is lower than the rate in 2016 (23.6 per 100,000), however, this rate has fluctuated since 2007 (Table 2). The TB incidence rate in First Nations persons with status living on-reserve in 2017 was 21.7 cases per 100,000, a decrease from the previous year (33.9 per 100,000). Similarly, the incidence rate in First Nations persons with status living off-reserve in 2017 decreased to 9.6 cases per 100,000 from 14.5 per 100,000 in 2016 (Table 2). In 2017, there were 142 cases among the Inuit compared to 113 cases in 2016, representing a 25.7% increase. The corresponding incidence rate increased from 168.7 in 2016 to 205.8 cases per 100,000 in 2017. Incidence rates among the Inuit population have ranged from a low of 85.2 per 100,000 population in 2007 to a high of 251.6 cases per 100,000 in 2012, but have consistently been higher than any other population subgroup since 2007 (Table 2).

Foreign born tuberculosis cases

Similar to previous years, foreign born persons carried the largest burden of TB disease in Canada in 2017 where 71.8% of total cases (n=1,290) were foreign born, corresponding to an incidence rate of 14.7 cases per 100,000 population. Although the incidence rate of TB among foreign born persons in Canada has remained relatively stable since 2007 (n=14.8 per 100,000 population), the absolute number of foreign born cases has steadily increased (Table 2). The number of foreign born cases increased from 1,224 in 2016 to 1,290 in 2017; however, the corresponding incidence rate decreased from 15.3 to 14.7 per 100,000 population.

Country of birth was reported for 97.4% (n=1,256) of these foreign born cases. Similar to 2016, the most commonly reported countries of origin among foreign born TB cases were the Philippines (n=276; 21.4%), India (n=262; 20.3%), China (n=186; 14.4%), Vietnam (n=60; 4.7%) and Pakistan (n=46; 3.6%).

Immigration status at the time of TB diagnosis was known for 63.3% (n=816) of foreign born TB cases reported in 2017. Of these, 77.7% (n=634) were Canadian citizens or permanent residents, 9.6% (n=78) were temporary residents (including students, visitors and workers), and 5.4% (n=44) were refugees, convention refugees and refugee claimants. Immigration status was reported as 'other' without further details for 7.4% of cases (n=60).

Year of arrival in Canada was reported for 91.0% (n=1,174) of foreign born TB cases in 2017. Of these, 36.1% (n=424) arrived within the past five years (between 2013 and 2017) and 17.7% (n=208) of these cases were diagnosed with TB within two years of arrival.

Diagnostic classification

In 2017, diagnostic classification was reported for 1,786 cases (99.4% of total TB cases). Of these, 1,403 (78.6%) were classified as respiratory TB and 383 (21.4%) were non-respiratory TB. Among respiratory TB cases, the most common site of disease was pulmonary (88.3%; n=1,239). Among non-respiratory TB

Table 2: Tuberculosis incidence rates and case counts by origin and year, Canada, 2007–2017

Origin		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Canadian born non-Indigenous	Cases	171	222	238	185	186	174	159	168	167	140	125
	Rate	0.7	0.9	1	0.7	0.7	0.7	0.6	0.6	0.6	0.6	0.5
Foreign born	Cases	1,067	1,064	1,063	1,054	1,108	1,112	1,153	1,110	1,177	1,224	1,290
	Rate	14.8	14.5	14.4	14.1	14.7	14.6	14.9	14.2	14.9	15.3	14.7
Canadian born Indigenous[a]	Cases	307	347	340	261	303	380	315	320	281	331	313
	Rate	23.9	26.2	24.9	18.6	20.7	24.4	19.9	20	17.1	23.3	21.5
First Nations (FN)[a,b]	Cases	229	232	227	121	177	208	205	182	157	208	154
	Rate	28.4	28.2	26.9	14.1	19.1	21.2	20.3	18	15.2	23.6	17.1
FN living on-reserve	Cases	129	119	122	109	99	113	148	106	101	149	97
	Rate	29.7	26.8	27	23.7	21.2	23.8	30.8	21.7	20.4	33.9	21.7
FN living off-reserve	Cases	83	98	87	73	66	80	50	68	51	56	38
	Rate	24.2	28	24.3	20	16.4	18.7	11.4	15.2	11.1	14.5	9.6
Métis[a]	Cases	32	27	25	26	21	11	18	19	12	10	17
	Rate	7.5	6.1	5.4	5.4	4.4	2.2	3.5	3.6	2.2	2.1	3.5
Inuit[a]	Cases	46	88	88	114	105	161	92	119	112	114	142
	Rate	85.2	160	157.1	200	166.7	251.6	139.4	177.6	164.7	170.1	205.8
Total Canada[c]	Cases	1,575	1,642	1,654	1,586	1,621	1,700	1,651	1,615	1,641	1,750	1,796
	Rate	4.8	4.9	4.9	4.7	4.7	4.9	4.7	4.5	4.6	4.8	4.9

[a] For 2016 and 2017, BC did not report Indigenous origin of TB cases
[b] Includes First Nations TB cases where residence on or off reserve was unknown, missing or not reported
[c] Includes TB cases were origin was unknown, missing or not reported

cases, the most common site of disease was the peripheral lymph nodes (50.7%; n=194). By origin, a larger proportion of Canadian born Indigenous cases had respiratory TB (93.9%) compared with Canadian born non-Indigenous (81.5%) and foreign born (74.3%) cases. Similar to previous years, respiratory TB was more common among male cases (83.2%) than female cases (72.7%) and in cases younger than 15 years (91.5%) compared with cases 15 years and older (77.2%).

Treatment outcomes for 2016

In 2016, 1,750 cases of TB were reported to the CTBRS. Of these, 98.6% (n=1,725) had a TB treatment outcome reported to the CTBRS in 2017. For the majority of these cases (80.2%) treatment was reported as successful (defined as having been cured of TB or having completed TB treatment). Death before or during treatment was reported for 7.6% of cases, where TB was reported to have contributed to or was the cause of death in approximately 60% of these cases. Treatment was reported as ongoing for an additional 5.3% of cases, and 3.0% of cases transferred out of the reporting treatment jurisdiction during treatment. Cases that were lost to follow-up or stopped treatment as a result of an adverse event comprised 0.6% of outcomes and treatment outcome was reported as unknown for 2.3% of cases.

TB treatment success was highest among Inuit and Métis cases, where 92.8% of Inuit cases and 88.9% of Métis cases were reportedly cured or had completed treatment. Treatment success rates were similar among First Nations (78.3%), foreign born (79.1%) and Canadian born non-Indigenous TB cases (78.0%).

Discussion

In 2017 there was a 2.6% increase in the number of reported cases of TB compared with 2016, and a corresponding increase in the incidence rate from 4.8 to 4.9 per 100,000 population. Since 2014, both the number of cases and incidence rate of TB have steadily increased. Despite these increases in recent years, the incidence rate has changed little since 2007, when it was 4.8 per 100,000 population. In 2017, Nunavut continued to have the highest rate of TB in Canada at 265.8 cases per 100,000, a rate which is nearly 70 times the national rate, whereas the highest concentration of cases was in Ontario (37.6%). While TB rates among foreign born individuals have been fairly stable in the last decade, this population continued to account for the majority of cases in 2017 at 71.8%. Among First Nations persons, the incidence rate of TB in 2017 (17.1 cases per 100,000) declined from 2016 (23.6 per 100,000); however, it was similar to 2015 (15.2 per 100,000) and 2014 (18.0 per 100,000). The rate among Inuit people in Canada in 2017 (205.8 cases per 100,000) was the highest it has been since 2012 (251.6 per 100,000). In 2017, an increase was also seen in the absolute number of cases reported among the Inuit compared to 2016, increasing from 113 to 142 cases in 2017. The majority of TB cases in Canada in 2017 were reported as respiratory TB (78.6%), with pulmonary TB (69.4%) being the most commonly reported diagnostic classification. For the majority of TB cases reported in 2016, TB treatment was successful (80.4%), reflecting effective treatment and high treatment adherence.

Based on these surveillance data alone, it is not known why there has been an increase in the number of TB cases in Canada over the last few years, but several things may be contributing to this. The increase in both the case count and incidence rate between 2016 and 2017 reflects the increases in both the foreign born and Inuit populations during this time period. While the incidence rate of TB in the foreign born population in Canada has been stable in recent years, the case count has steadily increased. This may, in part, be explained by the overall increase in the volume of migrants to Canada in recent years. Foreign born populations in Canada with latent TB infection (not contagious) can become ill with active TB disease years after the migration process or can become infected with TB during travel back to their countries of origin. Stressful living conditions, language and cultural barriers, food and housing insecurity are all factors that can increase the likelihood of reactivating a latent TB infection after migration (7). Increases in TB among the Inuit population are also attributable to an increased risk in this population of progressing from latent TB infection to active TB disease and to ongoing transmission of active TB, related to inequitable access to health care and the social determinants of health (4,7). As well, advances in TB detection, diagnosis and treatment have all recently been reported in Canada's north, which may be contributing to an increase in detection of TB cases among the Inuit (4).

Limitations

The limitations of the CTBRS have been described in detail previously (8). The CTBRS is a passive surveillance system and relies on receiving reports of active TB cases in Canada that are diagnosed by health care providers across the country and reported to provincial health authorities, and in turn, reported to PHAC. Completeness of case ascertainment and reporting delays are potential issues with this system; however, the WHO estimates that Canada's surveillance system has a case detection rate of 92% (12).

Finally, it is important to recognize that the data in this report are considered provisional and, as it continues to be updated annually, it are subject to change in future TB surveillance reports. If there are discrepancies between the data summarized in this report and provincial and territorial reports, the most recent provincial and territorial report should be used because updated national data may still be pending.

Conclusion

Tuberculosis surveillance data from 2017 continue to highlight well known trends in the epidemiology of TB in Canada; namely, that Indigenous and foreign born Canadians continue to be disproportionately represented among cases. Annual reporting of Canadian TB surveillance data is an important tool for informing TB prevention and control efforts and for monitoring progress on initiatives related to reducing the burden of TB in Canada, with the ultimate goal of TB elimination.

Authors' statement

ML – Conceptualization, methodology, software, validation, formal analysis, writing (original draft), supervision
HH – Conceptualization, software, validation, data curation, writing (review and editing)
NH – Conceptualization, software, validation, data curation, writing (review and editing)
MM – Writing (review and editing), supervision

Conflict of interest

None.

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Appendix: List of supplementary tables

Supplementary tables available upon request to:
phac.tb.surveillance.aspc@canada.ca

Supplementary Table 1: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population (all cases)—Canada and provinces/territories: 2007–2017

Supplementary Table 1M: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population (males)—Canada and provinces/territories: 2007–2017

Supplementary Table 1F: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population (females)—Canada and provinces/territories: 2007–2017

Supplementary Table 2: Reported new active and re-treatment tuberculosis cases and incidence rates per 100,000 population, by age group—Canada: 2007–2017

Supplementary Table 3: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population, by age group—Canada and provinces/territories: 2017

Supplementary Table 4: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population, by origin—Canada and provinces/territories: 2017

Supplementary Table 5: Tuberculosis incidence rates per 100,000 population, by origin—Canada, 2007–2017

Supplementary Table 6: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population, by main diagnostic classification—Canada, 2007–2017

Supplementary Table 7: Reported new active and re-treatment tuberculosis cases and incidence rate per 100,000 population, by main diagnostic classification—Canada and provinces/territories, 2017

Supplementary Table 8: Treatment outcome—Canada and provinces/territories: 2016

CANADIANS ARE STILL RELUCTANT TO GET TESTED FOR SEXUALLY TRANSMITTED AND BLOOD-BORNE INFECTIONS (STBBI)

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- information on risk factors

Discuss

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- available testing and treatment options
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*As reported in the Canadians' Awareness, Knowledge, and Attitudes Related to Sexually Transmitted and Blood-Borne Infections: 2018 Findings Report

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In the article "HIV in Canada – Surveillance Report 2017" published on December 6, 2018, the last sentences in the Results section describing data on perinatally HIV-exposed infants was incorrect as they described results for 2017 rather than the entire reporting period (1). They should have read:

"Between 1984–2017, 50.0% of perinatally HIV-exposed infants were from the Black race/ethnicity, while 23.3% were reported as Caucasian and 18.1% as Indigenous. The maternal region of birth for the majority of infants was North America (42.3%), followed by Africa (38.6%). The highest proportions of perinatally HIV-exposed infants were reported in Ontario (34.4%) and Quebec (25.3%)."

This was corrected on January 11, 2019.

Reference

1. Haddad N, Li JS, Totten S, McGuire M. HIV in Canada–Surveillance Report, 2017. Can Commun Dis Rep 2018;44(12): 348–56. DOI

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