

National Surveillance of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Annual Summary 2018

**Streptococcus and STI Unit
Bacterial Pathogens Division
National Microbiology Laboratory
Public Health Agency of Canada**

**Professional Guidelines and Public Health Practice
Division and
Surveillance and Epidemiology Division
Centre for Communicable Diseases and
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Public Health Agency of Canada**

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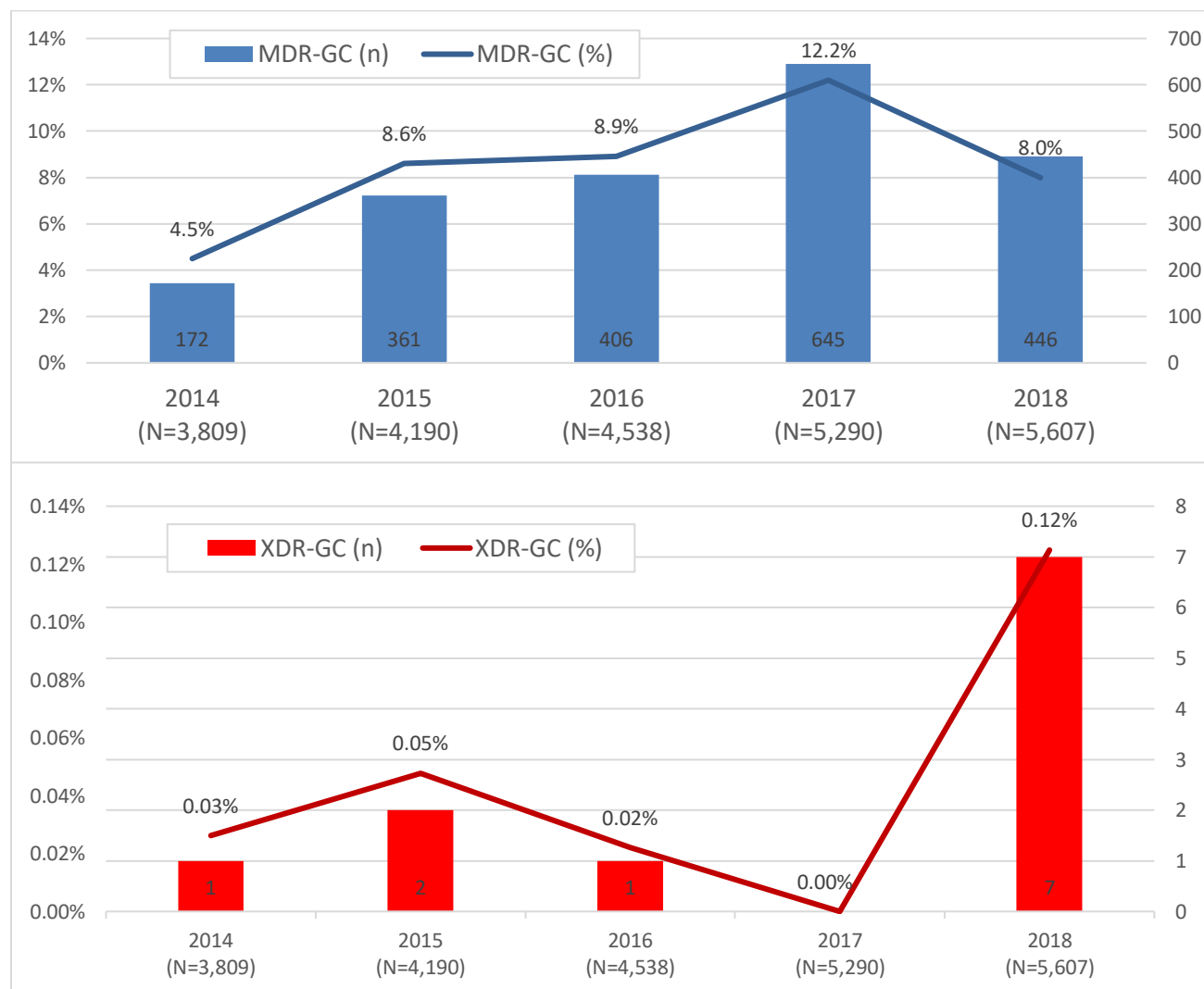
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ACRONYMS AND ABBREVIATIONS

AST	Antimicrobial Susceptibility Testing
AzR	Azithromycin Resistant <i>Neisseria gonorrhoeae</i>
CDC	Center for Disease Control, United States
CeDS	<i>Neisseria gonorrhoeae</i> with Decreased Susceptibility to Cefixime
CGSTI	Canadian Guidelines on Sexually Transmitted Infections
CipR	Ciprofloxacin Resistant <i>Neisseria gonorrhoeae</i>
CxDS	<i>Neisseria gonorrhoeae</i> with Decreased Susceptibility to Ceftriaxone
DS	Decreased Susceptibility
ESAG	Enhanced Surveillance of Antimicrobial Resistant Gonorrhea
GASP-Canada	Gonococcal Antimicrobial Surveillance Program - Canada
I	Intermediate
MDR-GC	Multidrug-resistant gonococci
MIC	Minimum inhibitory concentration
N	Denominator
NAAT	Nucleic acid amplification test
NG-MAST	<i>Neisseria gonorrhoeae</i> Multi Antigen Sequence Typing
NML	National Microbiology Laboratory
PenR	Penicillin Resistant <i>Neisseria gonorrhoeae</i>
PPNG	Penicillinase Producing <i>Neisseria gonorrhoeae</i>
R	Resistant
S	Susceptible
SpecR	Spectinomycin Resistant <i>Neisseria gonorrhoeae</i>
ST	Sequence Type
STI	Sexually Transmitted Infections
TetR	Tetracycline Resistant <i>Neisseria gonorrhoeae</i> (low level)
TRNG	Tetracycline Resistant <i>Neisseria gonorrhoeae</i> (high level)
WHO	World Health Organization
XDR-GC	Extensively drug-resistant gonococci

EXECUTIVE SUMMARY

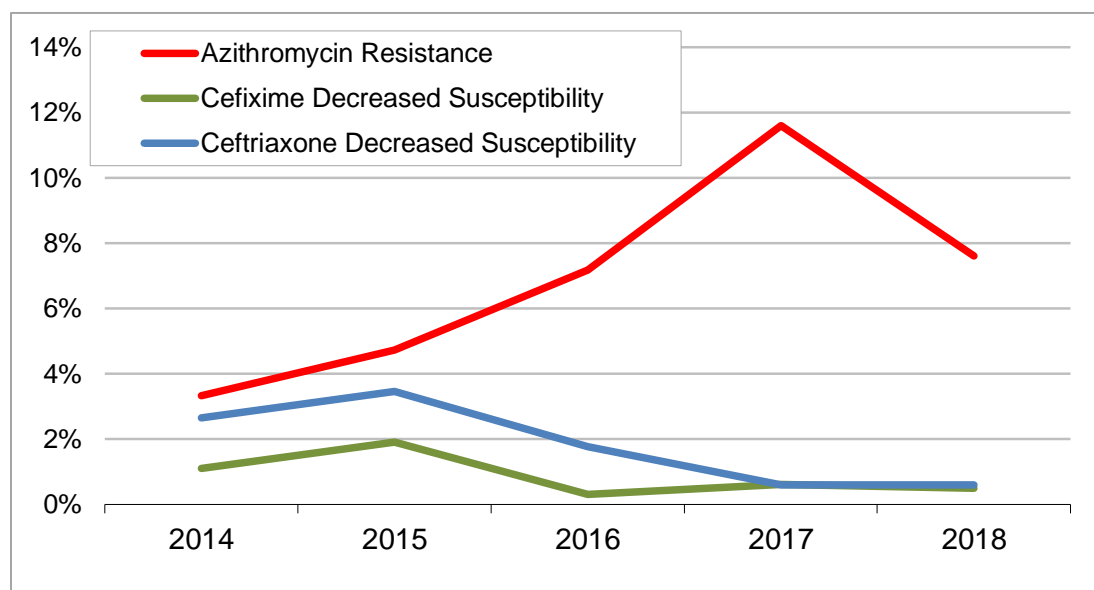
- This report consists of laboratory surveillance data for *Neisseria gonorrhoeae* isolates submitted by provincial microbiology laboratories to the National Microbiology Laboratory (NML) from 2014 – 2018 as part of the Gonococcal Antimicrobial Surveillance Program (GASP – Canada) .
- The Canadian reported rate of gonorrhea is on the rise and has more than doubled from 21.8 per 100,000 in 2001 to 79.5 cases per 100,000 in 2017. Gonorrhea is the second most commonly reported bacterial sexually transmitted infection in Canada with 29,034 cases reported in 2017.
- Over time, *N. gonorrhoeae* has acquired resistance to many antibiotics such as penicillin, tetracycline, erythromycin and ciprofloxacin. Antimicrobial resistance in *N. gonorrhoeae* is a serious threat to effective treatment of gonococcal infections. In 2018, 7 extensively drug resistant gonorrhea isolates (XDR-GC; decreased susceptibility to a cephalosporin plus resistance to azithromycin as well as resistance to at least two other antimicrobials) were identified in Canada posing a potential threat to successful treatment.
- In 2017, routine surveillance confirmed the first ceftriaxone resistant *N. gonorrhoeae* in Canada. In 2018, three ceftriaxone resistant cases were identified in Canada. All were associated with travel to South-East Asia.
- In 2018, a total of 5,607 *N. gonorrhoeae* isolates were cultured and tested in public health laboratories across Canada; 3,426 of these were submitted to the NML for antimicrobial susceptibility testing (AST). AST data for an additional 1,517 *N. gonorrhoeae* isolates were submitted by provincial public health laboratories and included in the analysis. The total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportions.
- The proportion of multi-drug resistant (MDR)-GC increased from 4.5% (172/3,809) in 2014 to 12.2% (645/5,290) in 2017 and then decreased to 8.0% (448/5,607) in 2018 (Figure A). These percentages represent the proportion of isolates with decreased susceptibility to the cephalosporins or resistance to azithromycin, along with resistance to at least two other antimicrobials.
- From 2014 to 2016, there were only 4 XDR-GC identified in Canada; none were found in 2017. In 2018, seven [1% (7/5,607)] isolates were classified as XDR-GC (Figure A).

Figure A. Trends of MDR-GC and XDR-GC *Neisseria gonorrhoeae* in Canada from 2014 to 2018^a

^aPercentage based on total number of isolates tested nationally: 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

- Isolates with decreased susceptibility to cefixime (MIC \geq 0.25 mg/L) decreased from 1.0% (38/3,809) in 2014 to 0.5% (27/5,607) in 2018 (Figure B).
- Isolates with decreased susceptibility to ceftriaxone (MIC \geq 0.125 mg/L) decreased from 2.5% (96/3,809) in 2014 to 0.6% (31/5,607) in 2018 (Figure B).
- The proportion of azithromycin resistant (MIC \geq 2mg/L) *N. gonorrhoeae* isolates increased from 3.4% (128/3,809) in 2014 to 7.6% (427/5,607) in 2018 (Figure B).
- Three high-level azithromycin resistant (MIC \geq 256 mg/L) *N. gonorrhoeae* isolates were identified in 2018 (QC, n=2; BC, n=1).

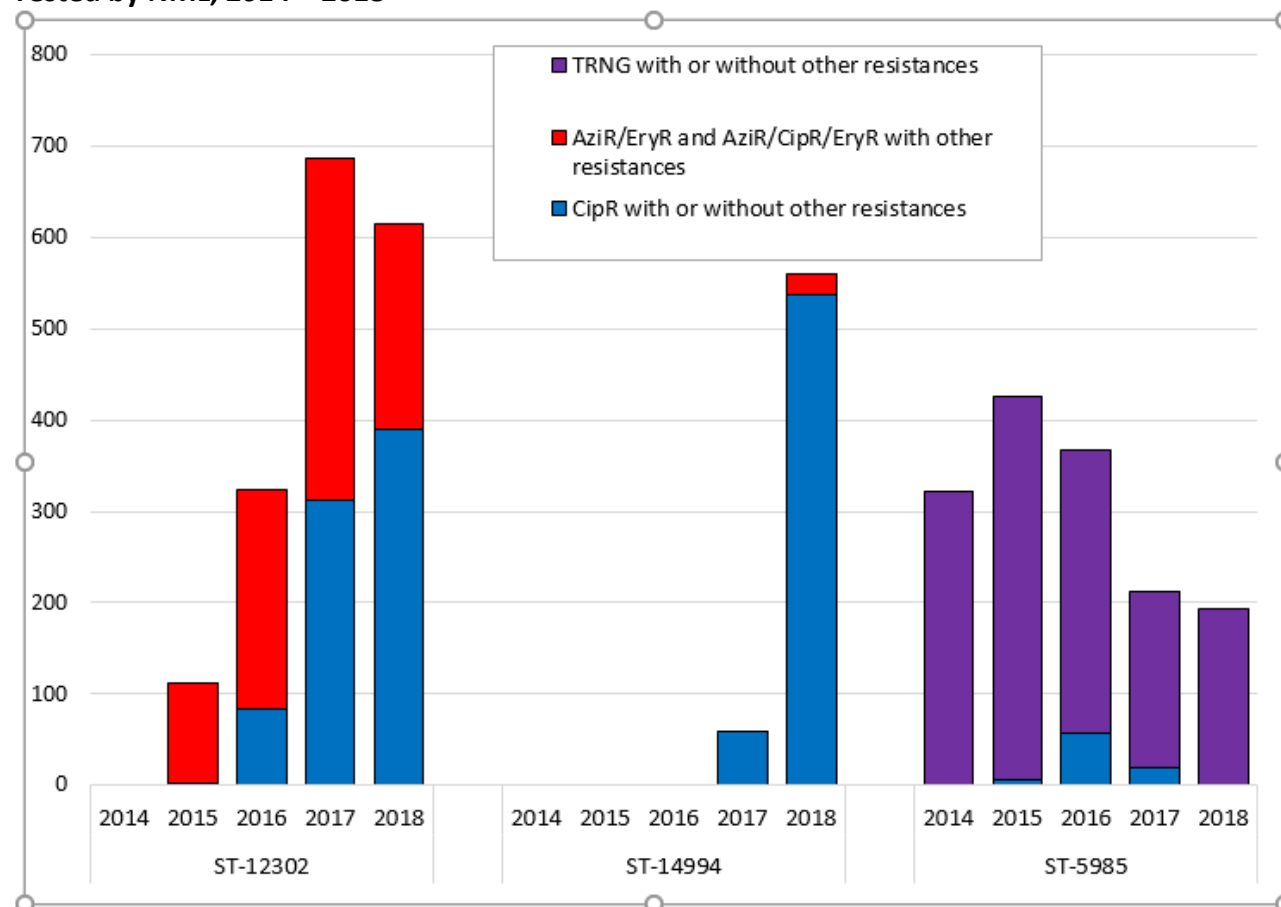
Figure B. Trends of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Tested in Canada, 2014-2018^a



^aPercentage based on total number of isolates tested nationally: 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

- In 2018, 57.3% (3,214/5,607) of isolates were resistant to ciprofloxacin; 56.0% (1,914/3,417) of the isolates were resistant to erythromycin; 9.2% (356/3,882) were resistant to penicillin; and 47.1% (2,640/5,607) were resistant to tetracycline.
- *N. gonorrhoeae* isolates submitted to the NML were also analyzed by molecular genotyping using the *N. gonorrhoeae* multi-antigen sequence type (NG-MAST) method. In 2018, 505 different sequence types (STs) were identified among the 3,375 isolates with STs identified and the most common sequence types were ST-12302 (18.2%), ST-14994 (16.6%), and ST-5985 (5.8%).
- ST-12302 increased from 4.3% of all isolates in 2015 to 24.1% in 2017 and has now decreased to 18.2% in 2018. In 2017, the isolates were primarily identified in central Canada; in 2018, approximately 10% were identified in western provinces (Figure C).
- ST-14994 was newly identified in 2017 (2.1% (60/2,875) and increased dramatically to 16.6% (562/3,379) in 2018 (Figure C). These isolates are resistant to multiple drugs including ciprofloxacin with approximately 5% of them having resistance to azithromycin as well.

Figure C. Trends of Prevalent NG-MAST Sequence Types of *Neisseria gonorrhoeae* Isolates Tested by NML, 2014 – 2018^a



^aA total of 378 sequence types were identified in 2014, 396 sequence types in 2015, 490 sequence types in 2016, 468 sequence types in 2017 and 503 sequence types in 2018. Only the most prevalent sequence types of 2014 to 2018 are represented in this graph.

For more details on the report and its key findings, please email: phac.nml.strepsti-lnm.strepits.aspc@canada.ca

INTRODUCTION

Neisseria gonorrhoeae is the causative agent of gonorrhoea and the second most commonly reported bacterial sexually transmitted infection (STI) in Canada, with 29,034 cases reported in 2017 (Public Health Agency of Canada, 2019). Rates of reported cases of gonorrhea have increased from 21.8 cases per 100,000 population in 2001 to 79.5 cases per 100,000 population in 2017 (Public Health Agency of Canada, 2019). Globally, gonorrhea is a public health threat with an estimated 78 million cases each year (Newman, 2015). In 2012, the World Health Organization released a global action plan to control the spread and impact of antimicrobial resistance in *N. gonorrhoeae* (World Health Organization, 2012) and the US CDC reported drug resistant *N. gonorrhoeae* at an urgent hazard level, requiring serious public health attention (Centres for Disease Control and Prevention, 2019). The treatment and control of gonorrhea is complicated by the ability of *N. gonorrhoeae* to evolve and develop resistance to many of the antibiotics used to treat it, including penicillins, tetracyclines, macrolides and quinolones (Hook, 2018). The emergence of isolates with decreased susceptibilities to the cephalosporins (Golparin, 2010; Ison, 2011; Pandori, 2009; Tapsall, 2010; World Health Organization, 2011) and reports of treatment failures in Canada (Allen, 2013) and around the world raise the possibility of gonorrhea infections becoming untreatable in the future. In 2017, routine surveillance confirmed the first ceftriaxone resistant *N. gonorrhoeae* in Canada (Lefebvre, 2018). In 2018, three additional ceftriaxone resistant *N. gonorrhoeae* were identified; one in Alberta (Smyczek, 2019, Berenger, 2019) and two in Ontario. Azithromycin resistance is also a concern. The emergence of high-level azithromycin resistant (≥ 256 mg/L) *N. gonorrhoeae* has been reported internationally (Chisholm, 2009) and isolates with this high level azithromycin resistance have also been identified in Canada.

In response to the increasing MICs and reports of cefixime treatment failures, the Canadian Guidelines on Sexually Transmitted Infections (CGSTI) updated gonorrhea treatment guidance to recommend combination therapy with 2 antibiotics. The CGSTI recommend 250 mg ceftriaxone intramuscularly and azithromycin 1 g orally as first-line treatment of pharyngeal infections and uncomplicated anogenital infections in gay/bisexual men who have sex with men. Additional information on the treatment of gonococcal infection is available at: <https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-34.html>

In 2009 (Tapsall, 2009), definitions were established for extensively drug-resistant gonococci (XDR-GC) and multidrug-resistant gonococci (MDR-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.

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)

A challenge to the laboratories monitoring antimicrobial susceptibilities of gonorrhea is that the number of cultures available for antimicrobial susceptibility testing is on the decline due to the shift from the use of culture to nucleic acid amplification test (NAAT) for the diagnosis of gonorrhea (Figure 1). This is of concern as *N. gonorrhoeae* cultures are required for antimicrobial susceptibility testing. Some jurisdictions in Canada no longer maintain the capacity to culture this organism and therefore antimicrobial susceptibility data in these jurisdictions are not available. In fact, over 80% of gonococcal infections in Canada are now diagnosed using NAAT.

The Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea (GASP) was initiated in 2014 to make improvements to the current surveillance program. This sentinel public health practice and surveillance study for *N. gonorrhoeae* collects integrated practice, epidemiological and laboratory information. The objectives of the study are to determine the trends and characteristics of antimicrobial resistance in *N. gonorrhoeae*, antimicrobial use and treatment failure. Both susceptible and resistant strains of gonorrhea are characterized in order to understand how strains spread in various populations in Canada and to inform Canadian guidance on STI management.

In this report, we present national-level trends in antimicrobial susceptibilities of *N. gonorrhoeae* collected from 2014 to 2018, applying the updated MDR-GC and XDR-GC definitions.

METHODS

In 2018, as part of the passive Gonococcal Antimicrobial Surveillance Program (GASP – Canada), provincial public health laboratories submitted a total of 3,426 viable *N. gonorrhoeae* isolates to the NML for antimicrobial susceptibility testing (AST). AST data for an additional 1,517 *N. gonorrhoeae* isolates (excluding duplicates) were submitted by provincial public health laboratories and included in the analysis. The total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportion. Table 1 presents the overall submission rate for resistance testing from the different provinces across Canada and the overall percentage of isolates resistant to at least one antibiotic.

N. gonorrhoeae isolates are submitted to the NML primarily when the provincial laboratories identify resistance/decreased susceptibility to at least one antibiotic or if the provincial laboratories do not perform any antimicrobial susceptibility testing. Submission of isolates is voluntary and is not standardized across the country and therefore the overall interpretation of the results is difficult due to the limitations related to the isolates available for testing. In 2018, MIC data generated by certain provinces was incorporated into our analysis. Alberta sent all of their resistant gonococci (n=837) to the NML for testing and submitted their AST data for the remaining isolates (n=200). Quebec (n=805) and British Columbia (n=219) only sent isolates to the NML for testing that met the following criteria:

- i) resistant to azithromycin
- ii) decreased susceptibility to cefixime and/or ceftriaxone
- iii) approaching resistance/decreased susceptibility to these antimicrobials

The AST data for the remaining isolates were submitted to the NML for analysis; Quebec n=1,060 and British Columbia n= 296.

To standardize the susceptibility testing results between laboratories, proficiency surveys were distributed by the NML annually. Minimum inhibitory concentration, or MIC (the minimum concentration of antibiotic that will inhibit the growth of the organism) was determined using agar dilution, and interpretations were based on the criteria outlined in Table 2. Resistance characterization definitions are provided in Table 3.

In addition to the isolates, information on age and gender of the patient and anatomical site of infection were also submitted to the NML (Tables 4 & 5).

Isolates were characterized by production of β -lactamase and the presence of *tetM* determinant (causing high-level tetracycline resistance) by PCR. *N. gonorrhoeae* isolates were also analyzed by molecular genotyping using the *N. gonorrhoeae* multi-antigen sequence type (NG-MAST) method (Martin, 2004) that incorporates the amplification of the porin gene (*por*) and the transferrin-binding protein gene (*tbpB*). DNA sequences of both strands were edited, assembled and compared using DNASTar, Inc. software. The resulting sequences were submitted to the NG-MAST website (<http://www.ng-mast.net/>) to determine the sequence types (ST).

Table 1. A Summary of the *Neisseria gonorrhoeae* culture isolates received by the NML, 2014 - 2018^{ab}

Province ^a	2014	2015	2016	2017	2018	Total
British Columbia	375	408	370	303	219	1,971
-submitted data	-	-	-	-	296	
Alberta	382	608	624	471	837	3,573
-submitted data	-	-	-	451	200	
Saskatchewan	93	64	91	125	135	508
Manitoba	46	58	89	143	195	531
Ontario	893	1,139	1,119	1,338	1,370	5,859
Québec	432	549	930	620	805	5,299
-submitted data	-	-	-	903	1,060	
Nova Scotia	15	16	33	33	35	132
Other ^b	12	14	8	21	19	74
Total isolates with available data	2,248	2,856	3,264	4,408	5,171	17,947
Total isolates analyzed for report^c	2,101	2,638	3,092	4,143	4,943	16,917
Total isolates resistant to at least one antibiotic	1,995	2,530	2,933	3,356	4,061	14,875
Total number of isolates tested in each province^d	3,809	4,190	4,538	5,290	5,607	23,434
Percentage of isolates resistant to at least one antibiotic	52.4%	60.4%	64.6%	63.4%	72.4%	63.5%
Percentage of total cases tested	23.4%	21.1%	19.1%	18.2%	19.3%^d	19.9%^d
Total cases reported in Canada	16,285	19,845	23,708	29,034	29,034^e	117,906^e

^aNunavut and the Yukon did not report or send any *Neisseria gonorrhoeae* cultures to the NML from 2014 to 2018

^bOther includes New Brunswick, Newfoundland, Prince Edward Island and Northwest Territories

^cIsolates that were duplicates (from same patient and same collection date or treatment failures), contaminated or did not grow were excluded.

^dTotal number of isolates tested by the provincial laboratories is used as the denominator in all % resistance calculations.

^e2018 total cases reported in Canada is estimated based on 2017 numbers.

Table 2. *Neisseria gonorrhoeae* Antimicrobial Resistance Criteria^{ab}

Antibiotic	Recommended Testing Concentration Ranges (mg/L)	MIC Interpretive Standard (mg/L) ^b				Sources of Antibiotics
		S	DS	I	R	
Penicillin	0.032 – 128.0	≤ 0.06	-	0.12-1.0	≥ 2.0	Sigma
Tetracycline	0.064 – 64.0	≤ 0.25	-	0.5 - 1.0	≥ 2.0	Sigma
Erythromycin	0.032 – 32.0	≤ 1.0	-	-	≥ 2.0	Sigma
Spectinomycin	4.0 – 256.0	≤ 32.0	-	64.0	≥ 128.0	Sigma
Ciprofloxacin	0.001 – 64.0	≤ 0.06	-	0.12 - 0.5	≥ 1.0	Sigma
Ceftriaxone	0.001 – 2.0	-	≥ 0.125	-	-	Sigma
Cefixime	0.002 – 2.0	-	≥ 0.25	-	-	Sigma
Azithromycin	0.016 – 32.0	≤ 1.0	-	-	≥ 2.0	Sigma
Ertapenem	0.002 - 2.0	-	≥ 0.063 (NS)	-	-	Sequoia
Gentamicin	0.5 - 128	≤ 4.0	-	8 - 16	≥ 32.0	Sigma

^aMIC Interpretative standards as recommended by the Clinical and Laboratory Standards Institute (CLSI M100, 2019) except for erythromycin (Ehret, 1996), ceftriaxone and cefixime (World Health Organization, 2012), ertapenem (Unemo, 2009) and gentamicin (Brown, 2010 & Daly, 1997).

^bS= Susceptible, I=Intermediate, R= Resistant, DS= Decreased susceptibility, NS=Non-susceptible

Table 3. *Neisseria gonorrhoeae* Antimicrobial Resistance Characterization Definitions

Characterization	Definition	Description
MDR-GC	Multidrug-resistant gonococci	Decreased susceptibility/Resistance to one currently recommended therapy (cephalosporin OR azithromycin) PLUS resistance to at least 2 other antimicrobials (penicillin, tetracycline, erythromycin, ciprofloxacin)
XDR-GC	Extensively drug-resistant gonococci	Decreased susceptibility/Resistance to two currently recommended therapies (cephalosporin AND azithromycin) plus resistance to at least two other antimicrobials (penicillin, tetracycline, erythromycin, ciprofloxacin)
TRNG	Tetracycline Resistant <i>Neisseria gonorrhoeae</i> (High-level)	Tet MIC ≥ 16.0 mg/L, TetM PCR positive
PPNG	Penicillinase Producing <i>Neisseria gonorrhoeae</i>	Pen MIC ≥ 2.0 mg/L, β -lactamase positive
PenR	Penicillin Resistant <i>Neisseria gonorrhoeae</i>	Pen MIC ≥ 2.0 mg/L, β -lactamase negative
TetR	Tetracycline Resistant <i>Neisseria gonorrhoeae</i> (Low-level)	Tet MIC ≥ 2.0 mg/L but ≤ 8.0 mg/L
EryR	Erythromycin Resistant <i>Neisseria gonorrhoeae</i>	Ery MIC ≥ 2.0 mg/L
CipR	Ciprofloxacin Resistant <i>Neisseria gonorrhoeae</i>	Cip MIC ≥ 1.0 mg/L
AzR	Azithromycin Resistant <i>Neisseria gonorrhoeae</i>	Az MIC ≥ 2.0 mg/L
SpecR	Spectinomycin Resistant <i>Neisseria gonorrhoeae</i>	Spec MIC ≥ 128 mg/L
CxDS	<i>Neisseria gonorrhoeae</i> with Decreased Susceptibility to Ceftriaxone	Cx MIC ≥ 0.125 mg/L
CeDS	<i>Neisseria gonorrhoeae</i> with Decreased Susceptibility to Cefixime	Ce MIC ≥ 0.25 mg/L

RESULTS AND DISCUSSION

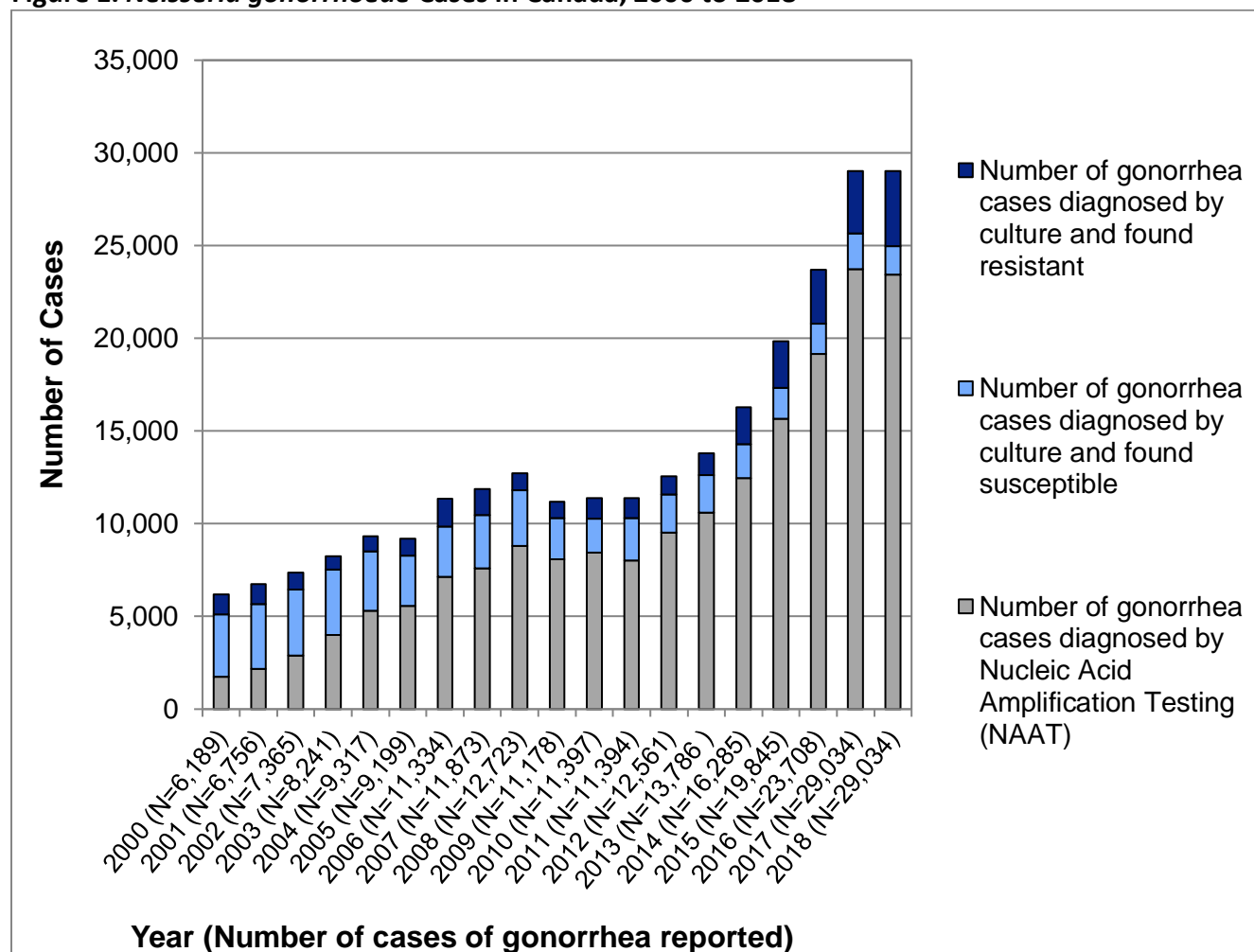
In 2018, a total of 5,607 *N. gonorrhoeae* isolates were cultured in public health laboratories across Canada; 3,426 of these were submitted to the NML and found viable for antimicrobial susceptibility testing (duplicates were excluded). AST and demographic data for another 1,517 unique isolates were submitted to the NML for a total of 4,943 isolates (3,426 + 1,517) to include in the 2018 analysis. A total of 4,061 of isolates tested across Canada were found to be resistant to at least one antibiotic (72.4%, 4,061/5,607) (Figure 1). Of all the gonorrhea cases reported in 2018, over 80% were diagnosed by NAAT for which there is no antimicrobial susceptibility data.

Gender and age data were available for 99.3% (4,907/4,943) of isolates/data submitted to the NML (Table 4). Of these, 84.3% (4,167/4,943) were males ranging from infancy to 77 years of age. A total of 15.0% (740/4,943) of isolates were from females ranging from infancy to 69 years.

Anatomic source data was available for 99.3% (4,907/4,943) of the isolates/data submitted to the NML (Table 4). Of these, 50.2% (2,480/4,943) were urethral, 19.1% (945/4,943) were rectal, 18.8% (930/4,943) were from the throat, 5.5% (273/4,943) were cervical, 2.5% (126/4,943) were vaginal, 0.7% (36/4,943) were ocular, 0.3% (14/4,943) were from blood and 2.8% (138/4,943) were from other sources.

Table 4. Age of patient and isolation site of the *Neisseria gonorrhoeae* isolates tested at the NML, 2018 (N=4,943)

Patient characteristics	Male	Female	Not Given	Total
Age	no. (%)	no. (%)	no. (%)	no. (%)
Under 15	5 (0.1)	21 (0.4)	0 (0)	26 (0.5)
15 - 20	262 (5.3)	139 (2.8)	2 (0)	403 (8.2)
21 - 25	860 (17.4)	204 (4.1)	4 (0.1)	1068 (21.6)
26 - 30	968 (19.6)	142 (2.9)	3 (0.1)	1113 (22.5)
31 - 40	1188 (24)	148 (3)	5 (0.1)	1341 (27.1)
41 - 50	512 (10.4)	49 (1)	2 (0)	563 (11.4)
51 - 60	284 (5.7)	30 (0.6)	1 (0)	315 (6.4)
60 +	86 (1.7)	6 (0.1)	2 (0)	94 (1.9)
Not Specified	2 (0)	1 (0)	17 (0.3)	20 (0.4)
Total	4167 (84.3)	740 (15)	36 (0.7)	4943 (100)
Isolation Site				
Penis/ Urethra	2453 (49.6)	11 (0.2)	16 (0.3)	2480 (50.2)
Rectum	867 (17.5)	75 (1.5)	3 (0.1)	945 (19.1)
Throat	717 (14.5)	205 (4.1)	8 (0.2)	930 (18.8)
Cervix	5 (0.1)	266 (5.4)	2 (0)	273 (5.5)
Vagina	3 (0.1)	122 (2.5)	1 (0)	126 (2.5)
Eye	21 (0.4)	15 (0.3)	0 (0)	36 (0.7)
Blood	5 (0.1)	7 (0.1)	2 (0)	14 (0.3)
Other	95 (1.9)	39 (0.8)	4 (0.1)	138 (2.8)
Not Specified	1 (0)	0 (0)	0 (0)	1 (0)
Total	4167 (84.3)	740 (15)	36 (0.7)	4943 (100)

Figure 1. *Neisseria gonorrhoeae* Cases in Canada, 2000 to 2018^a

^a2018 total cases estimated based on 2017 numbers.

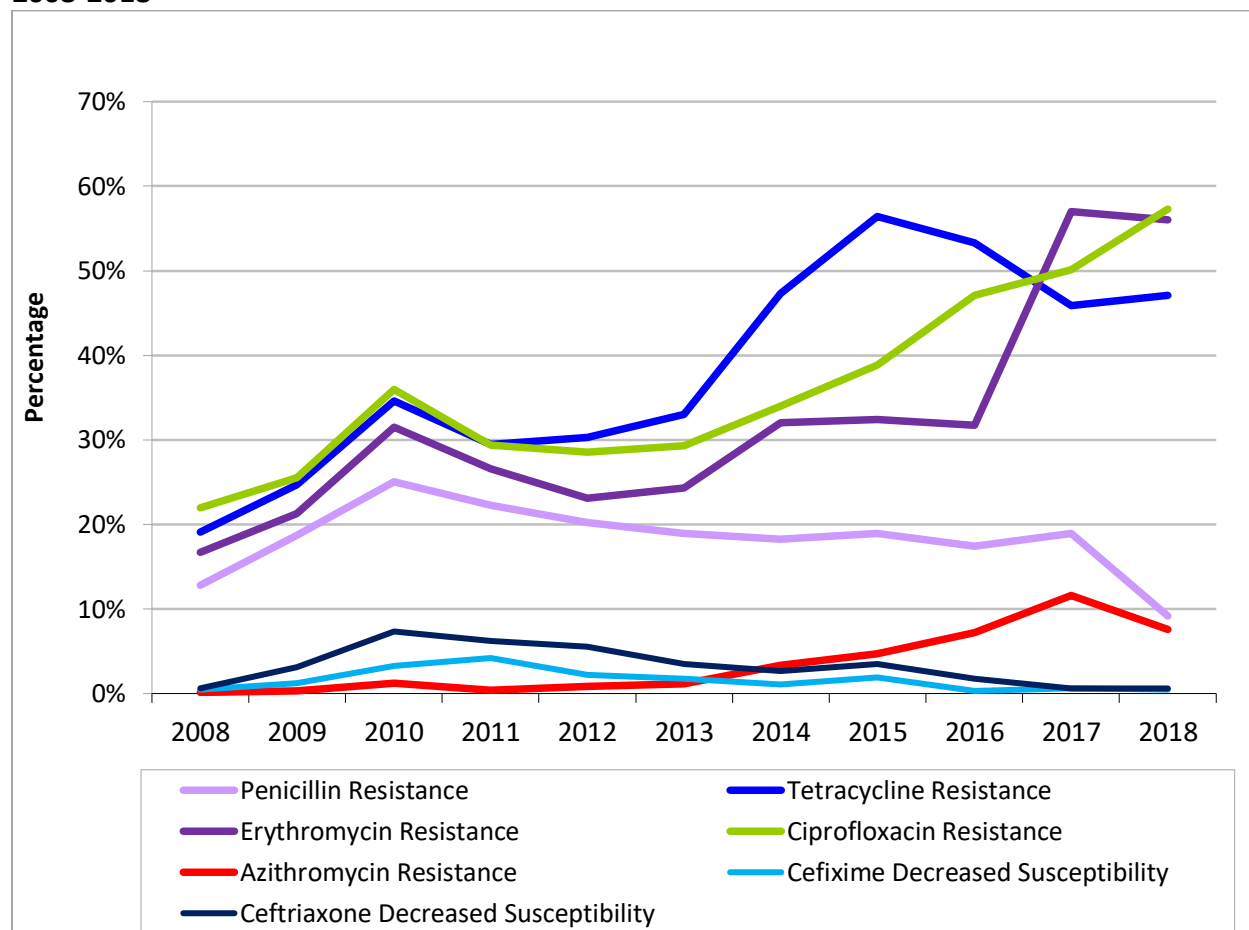
TRENDS IN ANTIMICROBIAL SENSITIVITIES

Figure 2 represents the trends of antimicrobial susceptibilities of *N. gonorrhoeae* tested in Canada from 2008 to 2018. In 2017, we started using provincial data (MICs) of isolates that were not sent to the NML in our analysis of antimicrobial susceptibilities. Submitting provinces do not test with all the antimicrobials being tested at the NML; therefore, we have adjusted the denominators for penicillin, erythromycin and spectinomycin to include only isolates tested with these antibiotics.

Penicillin resistance increased from 12.8% (500/3,907) in 2008 to 25.1% (744/2,970) in 2010 and has since decreased to 9.2% (356/3,883) in 2018. Tetracycline resistance increased from 19.1% (746/3,907) in 2008 to 47.1% (2,639/5,607) in 2018. In 2008, 16.7% (653/3,907) of Canadian isolates were found to be erythromycin resistant. This percentage has increased to 56.0% (1,914/3,418) in 2018. The percentage of ciprofloxacin resistant isolates increased from 22.0% (858/3,907) in 2008 to 57.3% (2,652/5,607) in 2018. Azithromycin resistant *N. gonorrhoeae* have been slowly increasing since 2011 when it was 0.4% (13/3,360) to 1.2%

(37/3,195) in 2013. In 2014, the proportion increased to 3.3% (127/3,809) and has increased significantly ($p<0.001$) to 7.6% (427/5,607) in 2018. Decreased susceptibility to cefixime decreased slightly between 2017 [0.6% (31/5,290)] and 2018 [0.5% (27/5,607)] while decreased susceptibility to ceftriaxone increased from 0.5% (29/5,290) in 2017 to 0.6% (31/5,607) in 2018. Of the 15,395 viable isolates tested at NML between 2014 and 2018, none showed resistance to spectinomycin.

Figure 2. Trends of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Tested in Canada, 2008-2018^{ab}



^aPercentage based on total number of isolates tested nationally: 2008=3,907; 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

^b2017 and 2018 penicillin denominators are 3,267 and 3,883, respectively; erythromycin denominators are 2,879 and 3,418, respectively

MULTIDRUG-RESISTANT (MDR) AND EXTENSIVELY DRUG-RESISTANT (XDR) GONOCOCCI

The proportion of MDR-GC increased from 4.5% (172/3,809) in 2014 to 12.2% (645/5,290) in 2017 and then decreased to 8.0% (446/5,607) in 2018 (Figure 3). These percentages represent the proportion of isolates with decreased susceptibility to the cephalosporins or resistance to azithromycin, along with resistance to at least two other antimicrobials.

From 2014 to 2018, eleven cases of XDR-GC were identified in Canada. In 2014, only one XDR-GC was identified [0.03% (1/3,809)]; in 2015, two were detected [0.05% (2/4,190)]; in 2016, only one was isolated [0.02% (1/4,538)] and in 2017 no XDR-GC were identified. In 2018, however, the number of XDR-GC increased to seven (0.1%, 7/5,607) (Figure 3).

Figure 3. Trends of MDR-GC and XDR-GC *Neisseria gonorrhoeae* in Canada from 2014 to 2018^a

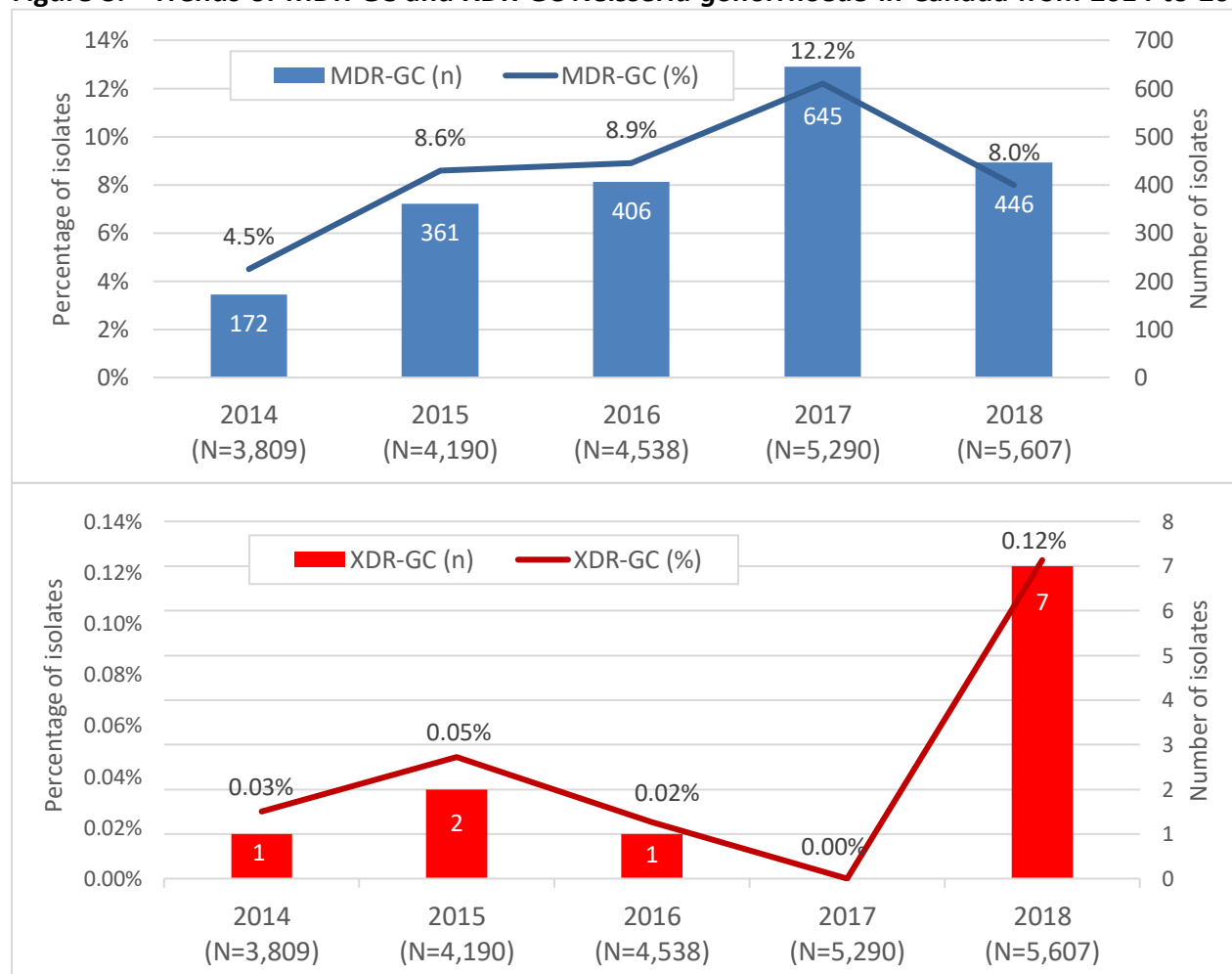
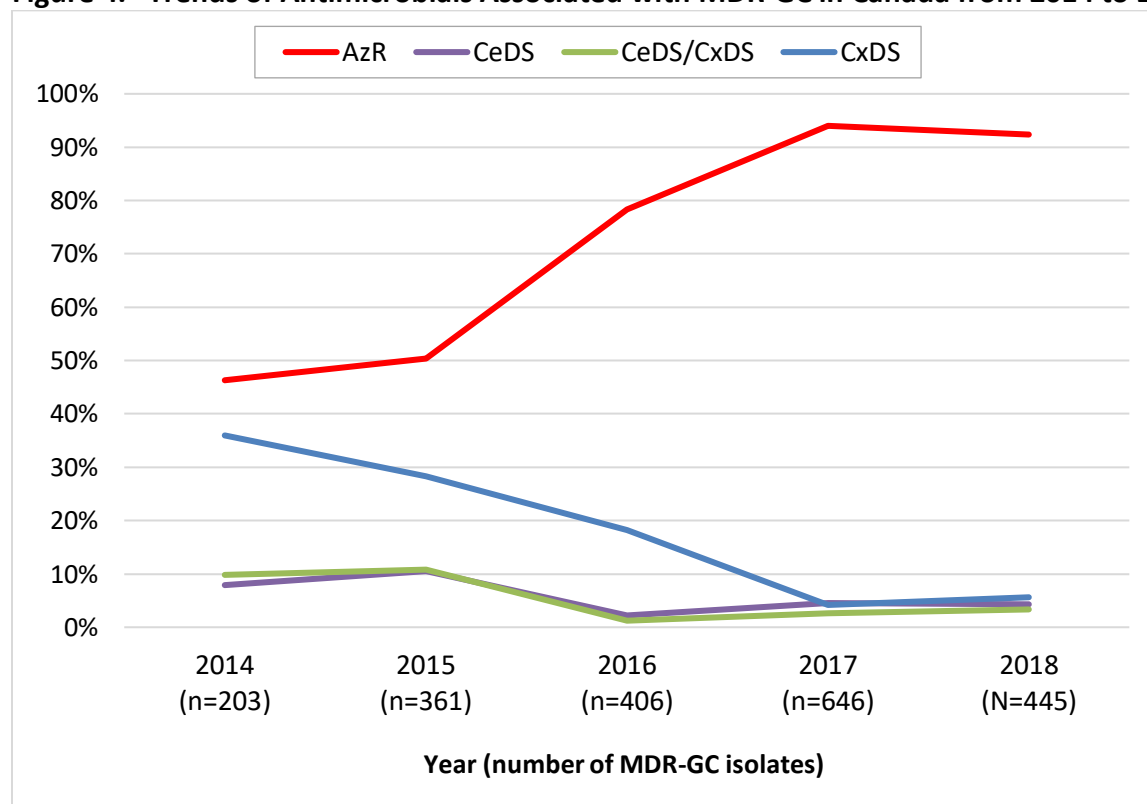


Figure 4 represents the trends of the antimicrobials associated with MDR-GC. MDR-GC with azithromycin resistance increased significantly ($p<0.001$) from 46.3% (94/203) in 2014 to 94.0% (607/646) in 2017. It decreased slightly in 2018 to 92.4% (411/445). Conversely, MDR-GC associated with decreased susceptibility to ceftriaxone declined significantly ($p<0.001$) from 36.0% (73/203) in 2014 to 5.6% (25/445) in 2018.

Figure 4. Trends of Antimicrobials Associated with MDR-GC in Canada from 2014 to 2018^a



THIRD GENERATION CEPHALOSPORINS

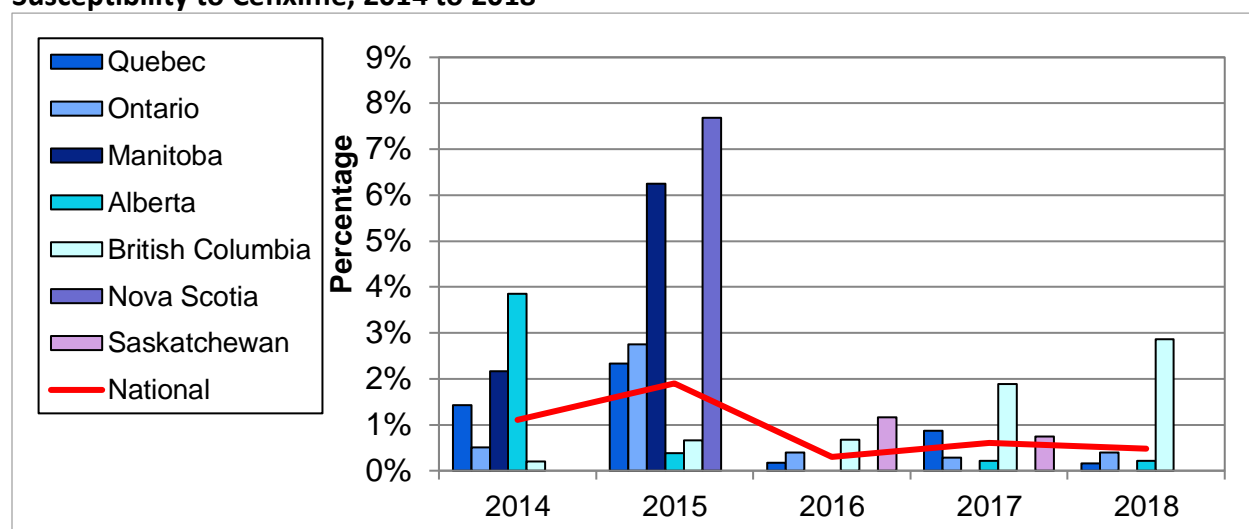
Based on WHO (2012) definitions (isolates with MIC ≥ 0.25 mg/L for cefixime and ≥ 0.125 mg/L for ceftriaxone have decreased susceptibility), 0.5% of isolates (27/5,607) were identified as having decreased susceptibility to cefixime (Figure 5) and 0.6% (31/5,607) were identified as having decreased susceptibility to ceftriaxone (Figure 6) in 2018. In 2017, 1 isolate with a cefixime MIC of 2 mg/L and a ceftriaxone MIC of 1 mg/L was identified in Quebec (Lefebvre, 2018). In 2018, 3 isolates with a cefixime MIC of 2 mg/L and a ceftriaxone MIC of 1 or 0.5 mg/L were identified in Alberta (n=1) (Berenger, 2019) and Ontario (n=2).

In 2018, 0.7% (37/5,607) of isolates had decreased susceptibility to cefixime and/or ceftriaxone. This number represents a slight decrease from 0.8% (43/5,290) in 2017.

The geographical distribution of *N. gonorrhoeae* isolates with decreased susceptibility/resistance to cefixime and ceftriaxone within Canada are represented in Figures 5 and 6 and in Tables 5 and 6.

The modal MIC for cefixime has decreased from to 0.016 mg/L in 2017 and 2018. The ceftriaxone modal MIC remained at 0.032 mg/L from 2014 to 2016 but decreased to 0.008 mg/L in 2018 (Figures 7-10, Tables 7 and 8).

Figure 5. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Cefixime, 2014 to 2018^a

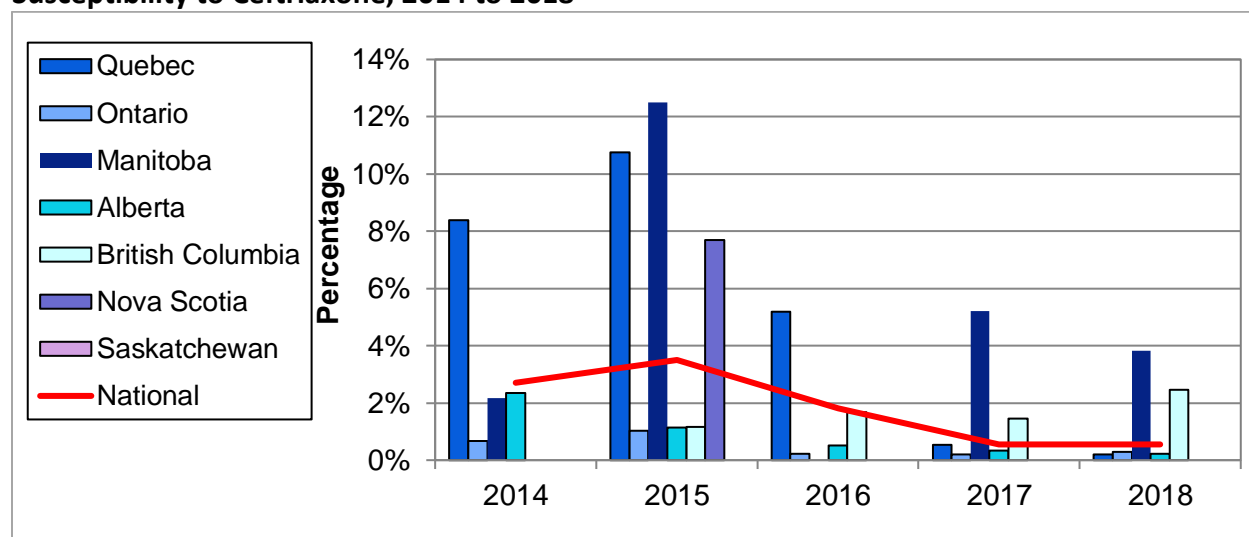


^aDenominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 5. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Cefixime, 2014 to 2018^a

Province	Year				
	2014	2015	2016	2017	2018
Quebec	13	23	2	13	3
Ontario	9	46	7	6	8
Manitoba	1	3	0	0	0
Alberta	18	3	0	2	2
British Columbia	1	4	4	9	14
Nova Scotia	0	1	0	0	0
Saskatchewan	0	0	1	1	0
Total No. of isolates	42	80	14	32	27
% CeDS of all isolates tested nationally	1.1%	1.9%	0.3%	0.6%	0.5%

^aPercentage based on total number of isolates tested nationally: 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

Figure 6. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Ceftriaxone, 2014 to 2018^{ab}

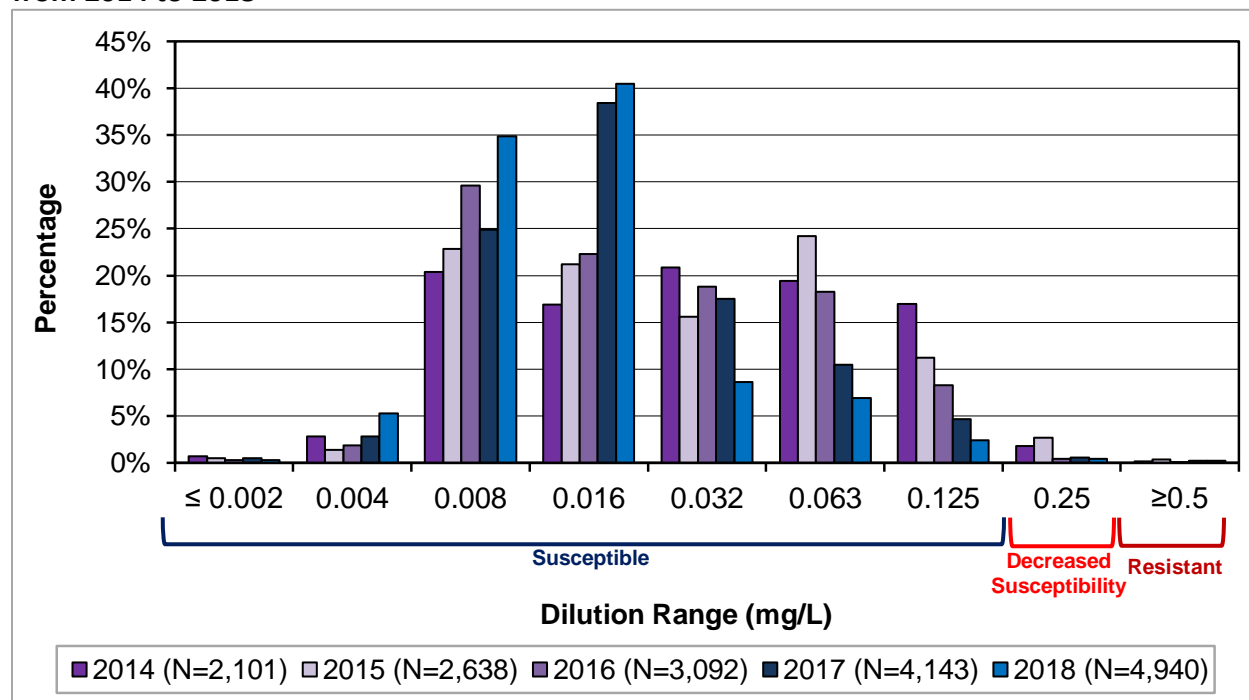
^aDenominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 6. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Ceftriaxone, 2014 to 2018^a

Province	Year				
	2014	2015	2016	2017	2018
Quebec	77	106	62	8	4
Ontario	12	17	4	4	6
Manitoba	1	6	0	7	7
Alberta	11	9	4	3	2
British Columbia	0	7	10	7	12
Nova Scotia	0	1	0	0	0
Saskatchewan	0	0	0	0	0
Total No. of isolates	101	146	80	29	31
% CxDS of all isolates tested nationally	2.7%	3.5%	1.8%	0.5%	0.6%

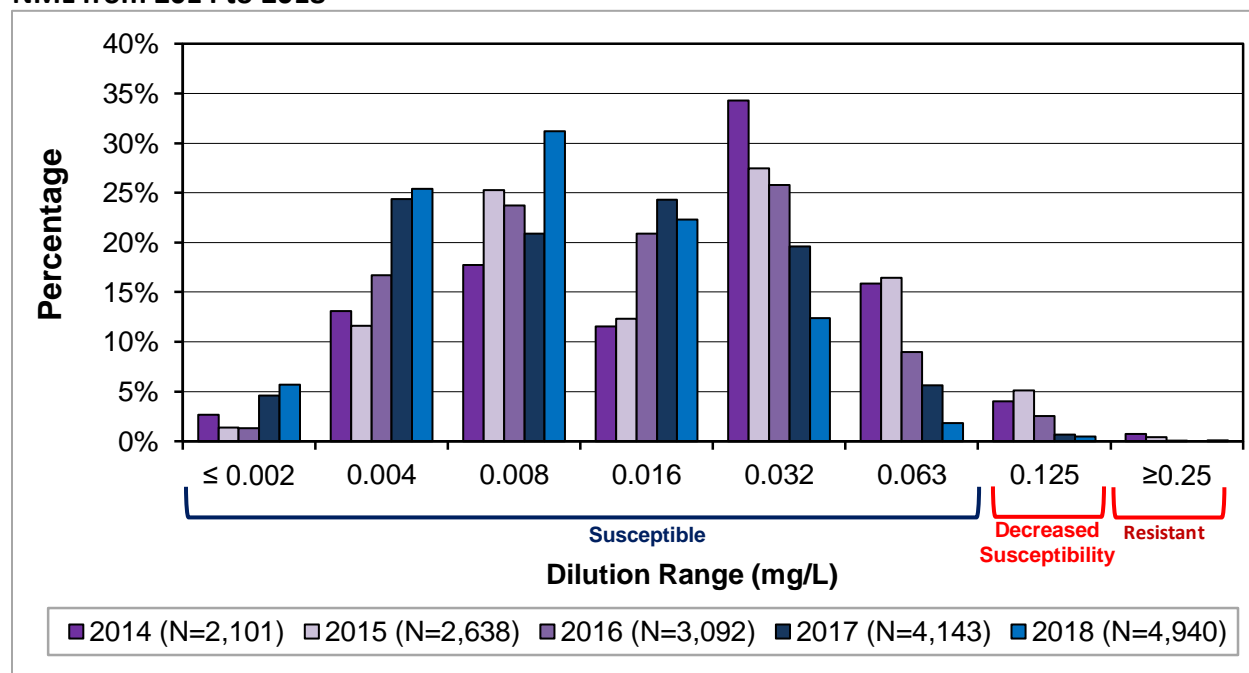
^aPercentage based on total number of isolates tested nationally: 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

Figure 7. Trends of Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a

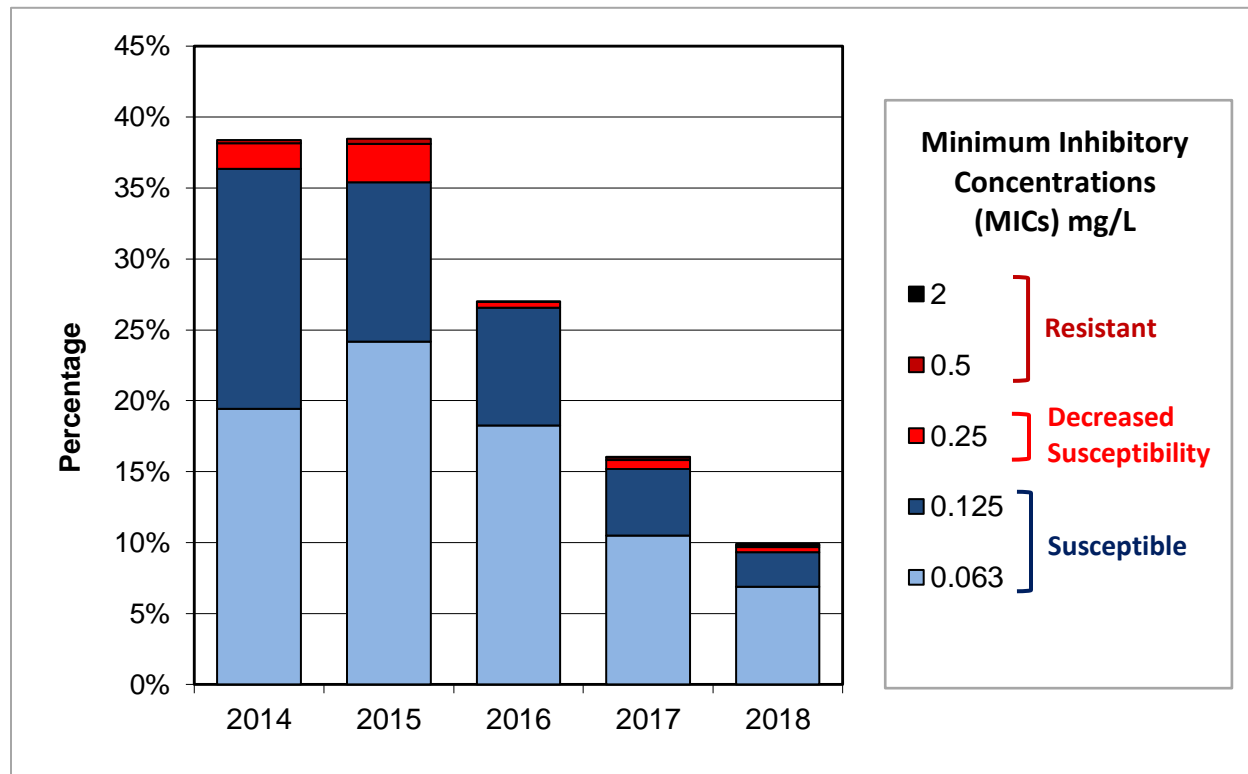


^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by NML as the denominator (N).

Figure 8. Trends of Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a



^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by NML as the denominator (N).

Figure 9. Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^{ab}

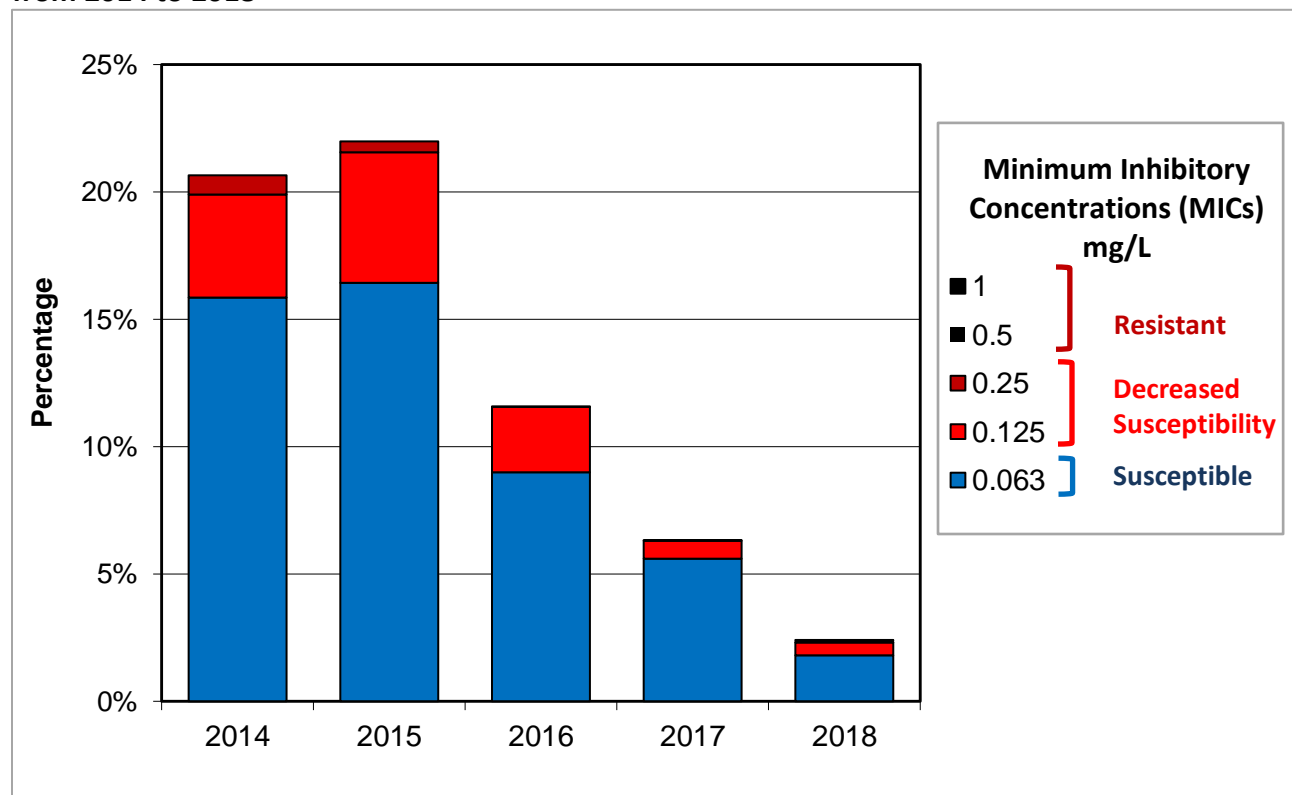
^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator: 2014=2,101; 2015=2,638; 2016=3,092; 2017=4,143; 2018=4,940

^bIsolates not represented on this chart had cefixime MICs <0.063 mg/L and were susceptible.

Table 7. Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a

Dilutions (mg/L)	Interpretive Category	Year				
		2014	2015	2016	2017	2018
≤0.032 mg/L	Susceptible	60.7%	61.6%	73.0%	84.0%	90.1%
0.063 mg/L		19.4%	24.2%	18.3%	10.5%	6.9%
0.125 mg/L		16.9%	11.3%	8.3%	4.7%	2.4%
0.25 mg/L	Decreased Susceptibility	1.8%	2.7%	0.4%	0.6%	0.4%
0.5 mg/L	Resistant	0.2%	0.3%	0.03%	0.2%	0.12%
2 mg/L		0%	0%	0%	0.02%	0.1%

^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2014=2,101; 2015=2,638; 2016=3,092; 2017=4,143; 2018=4,940

Figure 10. Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^{ab}

^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2014=2,101; 2015=2,638; 2016=3,092; 2017=4,143; 2018=4,940

^bOne isolate not represented on this chart had ceftriaxone MICs = 0.5 mg/L; other isolates not represented have MICs <0.063 mg/L and were susceptible.

Table 8. Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a

Dilutions (mg/L)	Interpretive Category	Year				
		2014	2015	2016	2017	2018
≤0.032 mg/L	Susceptible	78.2%	78.1%	88.4%	93.7%	97.6%
0.063 mg/L		15.9%	16.4%	9.0%	5.6%	1.8%
0.125 mg/L	Decreased Susceptibility	4.1%	5.1%	2.6%	0.7%	0.5%
0.25 mg/L		0.8%	0.4%	0.03%	0%	0.02%
0.5 mg/L	Resistant	0%	0%	0%	0%	0.04%
1 mg/L		0%	0%	0%	0.02%	0.02%

^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator: 2014=2,101; 2015=2,638; 2016=3,092; 2017=4,143; 2018=4,940

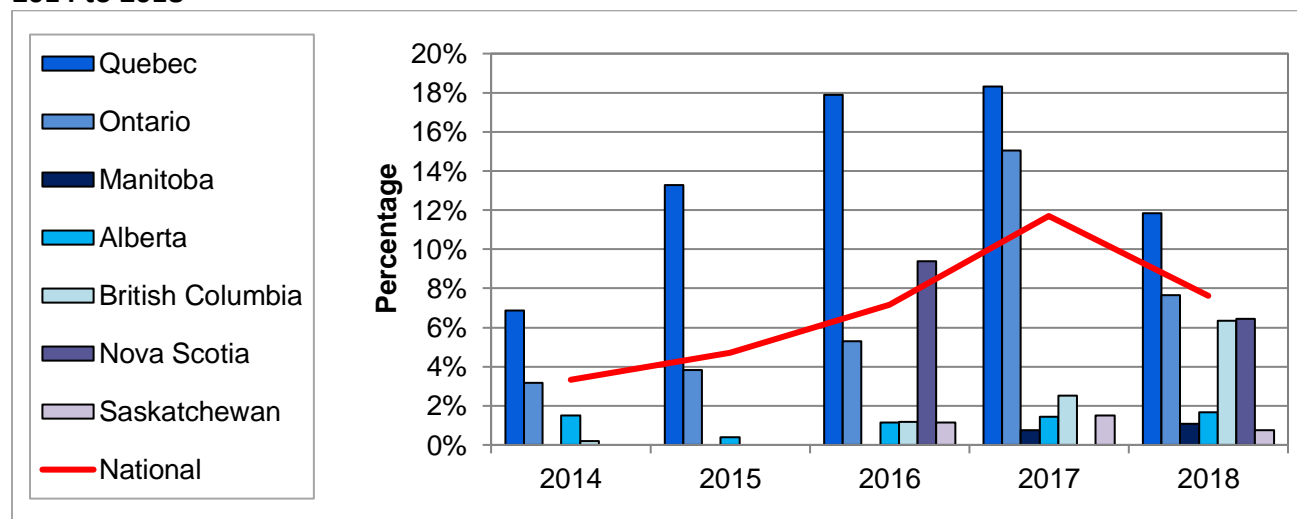
AZITHROMYCIN

The distribution of azithromycin resistant isolates across Canada is represented in Figure 11 and Table 9. Azithromycin resistant *N. gonorrhoeae* increased from 3.3% (127/2,101) in 2014 to 7.6% (427/5,607) in 2018.

The modal MIC for azithromycin was 0.25 mg/L from 2014 to 2018 (Figures 12 and 13 and Table 10), despite the greater number of resistant isolates since 2015. Isolates with an MIC of 2 mg/L (the breakpoint for azithromycin) increased from 0.8% (16/2,101) in 2014 to 13.6% (565/4,143) in 2017 but decreased to 7.4% (366/4,940) in 2018. Of concern is the number of strains with an MIC of 1 mg/L, which is just one MIC from the breakpoint and is considered to be within the acceptable range of error. These increased from 13.5% (560/4,143) in 2017 to 21.4% (1,057/4,940) in 2018.

In 2016, 1 isolate (QC) was identified with high-level azithromycin resistance (MIC \geq 256 mg/L). In 2017, 3 were identified (ON, QC, SK). In 2018, another three isolates with high level azithromycin resistance were identified in Canada (QC, n=2; BC, n=1).

Figure 11. Geographical Distribution of Azithromycin Resistant *Neisseria gonorrhoeae* Isolates, 2014 to 2018^a

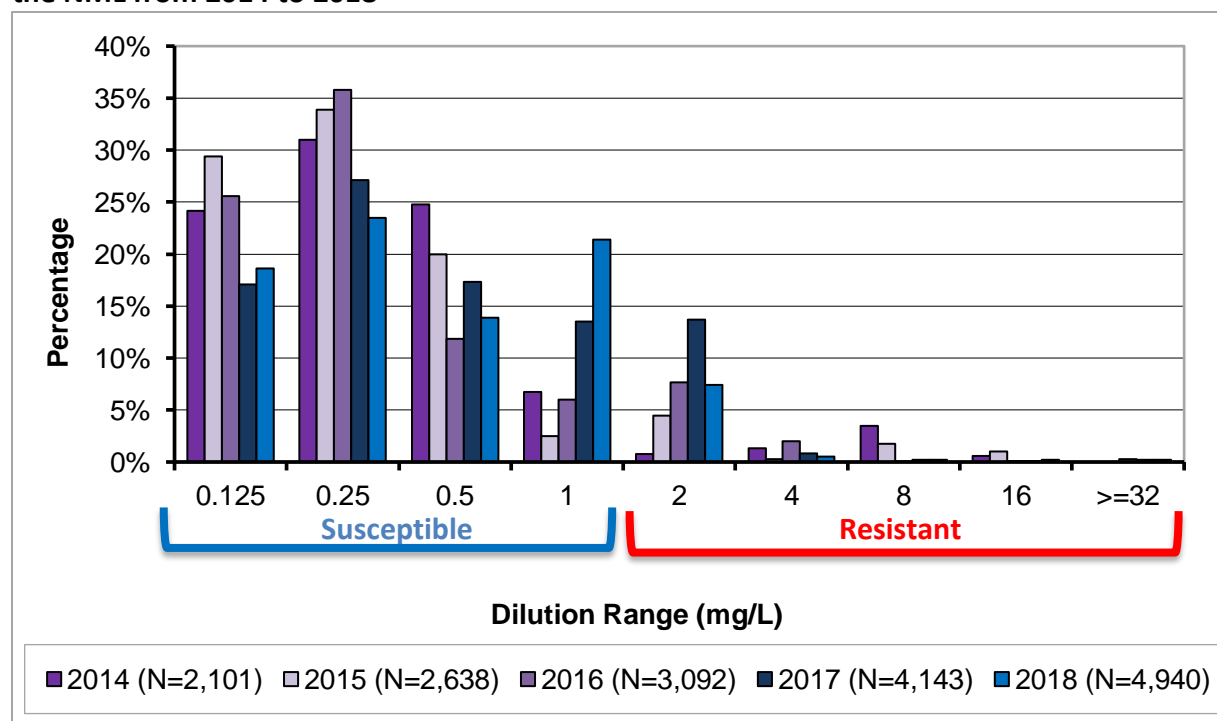


^aDenominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 9. Geographical Distribution of Azithromycin Resistant *Neisseria gonorrhoeae* Isolates, 2014 to 2018^a

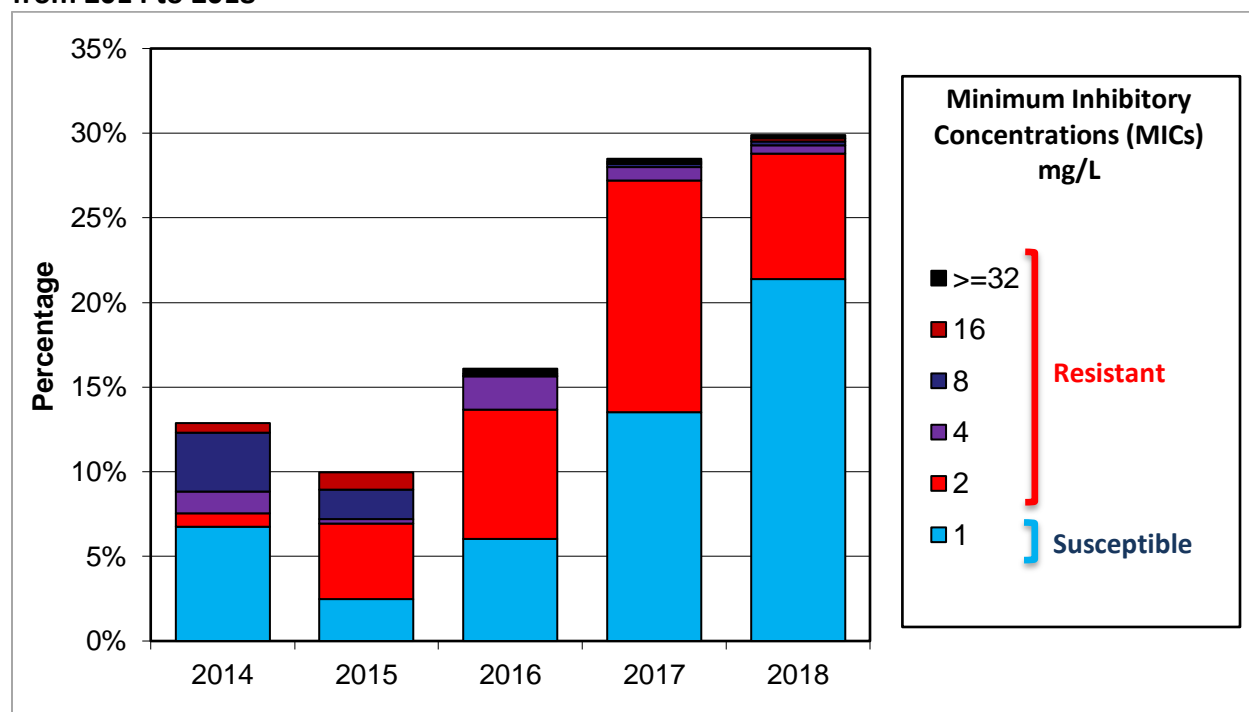
Province	Year				
	2014	2015	2016	2017	2018
Quebec	63	131	214	274	222
Ontario	56	64	92	317	152
Alberta	7	3	9	13	15
British Columbia	1	0	7	12	31
Nova Scotia	0	0	3	0	2
New Brunswick	0	0	0	1	2
Manitoba	0	0	0	1	2
Saskatchewan	6	0	1	2	1
Total No. of AzR isolates	127	198	326	620	427
% AzR of all isolates tested nationally	3.3%	4.7%	7.2%	11.7%	7.6%

^aPercentage based on total number of isolates tested nationally: 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

Figure 12. Trends of Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^{ab}

^aPercentages were calculated using the total number of viable strains (both resistant and susceptible isolates) tested by NML as the denominator (N).

^bIsolates not represented on this chart had azithromycin MICs <0.125 mg/L and were susceptible.

Figure 13. Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^{ab}

^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2014=2,101; 2015=2,638; 2016=3,092; 2017=4,143; 2018=4,940

^bIsolates not represented in this chart had azithromycin MICs <0.25mg/L and were susceptible.

Table 10. Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a

Dilution (mg/L)	Interpretive Category	Year				
		2014	2015	2016	2017	2018
≤0.5 mg/L	Susceptible	85.8%	90.0%	83.4%	71.6%	70.1%
1 mg/L		6.8%	2.5%	6.0%	13.4%	21.4%
2 mg/L	Resistant	0.8%	4.5%	7.7%	13.6%	7.4%
4 mg/L		1.3%	0.3%	2.0%	0.8%	0.5%
8 mg/L		3.5%	1.7%	0.03%	0.2%	0.2%
16 mg/L		0.6%	1.0%	0.1%	0.1%	0.2%
≥32 mg/L		0%	0%	0.3%	0.2%	0.2%

^aPercentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2014=2,101; 2015=2,638; 2016=3,092; 2017=4,143; 2018=4,940

CO-RESISTANCE – AZITHROMYCIN AND CEPHALOSPORINS

In 2012, seven isolates with a combined decreased susceptibility to cephalosporins and resistance to azithromycin (XDR-GC) were identified (0.2%, 7/3,036). These are the first isolates to identified in Canada with both decreased susceptibility to cephalosporins and resistance to azithromycin thus possibly threatening the success of currently recommended dual therapy treatment options. Although there was a slight increase in these isolates in 2013 (0.3%, 8/3,195), numbers were decreased from 2014 to 2017. In 2018, 7 isolates with both decreased susceptibility to cephalosporins and resistance to azithromycin were identified (0.12%, 7/5,607). They were all identified as ST-5308 with 5 from BC and 2 from QC (Table 11).

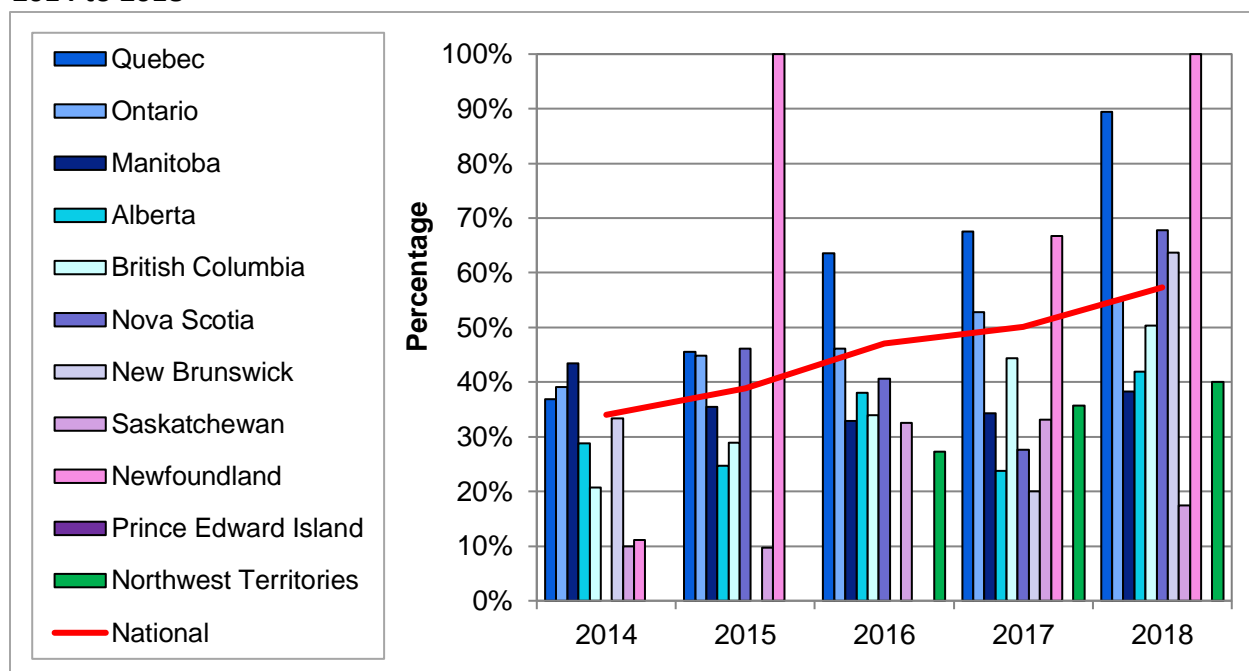
Table 11. *Neisseria gonorrhoeae* Isolates with Combined Decreased Susceptibility to Cephalosporins and Resistance to Azithromycin^a

Year	AzR Isolates		AzR Isolates with CeDS and/or CxDS				Provinces
	No.	% ^a	No.	% ^a	Isolation Sites	NG-MAST	
2012	26	0.9%	7	0.2%	Penis/Urethra (5); Rectum (1); Throat (1)	ST-3158 (6); ST-1407 (1)	BC (1), On (6)
2013	37	1.2%	8	0.3%	Penis/Urethra (5); Rectum (1); Throat (1); Cervix (1)	ST-3158 (6); ST-1407 (1); ST-9427 (1)	BC (2), SK (1), ON (5)
2014	127	3.3%	1	0.03%	Penis/Urethra	ST-1407	QC
2015	198	4.7%	2	0.05%	Penis/Urethra (1); Cervix (1)	ST-11765, ST-2400	ON, QC
2016	326	7.2%	1	0.02%	Rectum	ST-2318	BC
2017	624	11.7%	0	0%	n/a	n/a	n/a
2018	427	7.6%	7	0.12%	Throat (4); Penis/Urethra (2); Cervix (1)	ST-5308	BC (5), QC (2)

^aPercentage based on the number of isolates tested nationally: 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

CIPROFLOXACIN

The percentage of ciprofloxacin resistant isolates increased from 50.1% (2,652/5,290) in 2017 to 57.3% (3,214/5,607) in 2018. Percentages for each province are represented in Figure 14 and Table 12. Of the 3,214 ciprofloxacin resistant isolates identified in 2018, 71.6% (2,303/3,214) were also resistant to at least one other antibiotic; 13.3% (429/3,214) were characterized as MDR-GC and 0.2% (7/3,214) were XDR-GC.

Figure 14. Geographical Distribution of Ciprofloxacin Resistant *Neisseria gonorrhoeae* Isolates, 2014 to 2018^a

^aDenominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 12. Geographical Distribution of Ciprofloxacin Resistant *Neisseria gonorrhoeae* Isolates, 2014 to 2018^a

Province	Year				
	2014	2015	2016	2017	2018
Quebec	338	479	761	1,005	1,375
Ontario	690	750	800	1,114	1,092
Manitoba	20	17	28	46	70
Alberta	135	196	299	213	377
British Columbia	102	174	204	212	246
Nova Scotia	0	6	13	8	21
New Brunswick	1	0	0	2	7
Saskatchewan	9	6	28	44	23
Newfoundland	1	1	0	2	1
Prince Edward Island	0	0	0	0	0
Northwest Territories	0	0	3	5	2
Total No. of CipR isolates	1,296	1,629	2,136	2,652	3,214
%CipR of all isolates tested nationally	34.0%	38.9%	47.1%	50.1%	57.3%

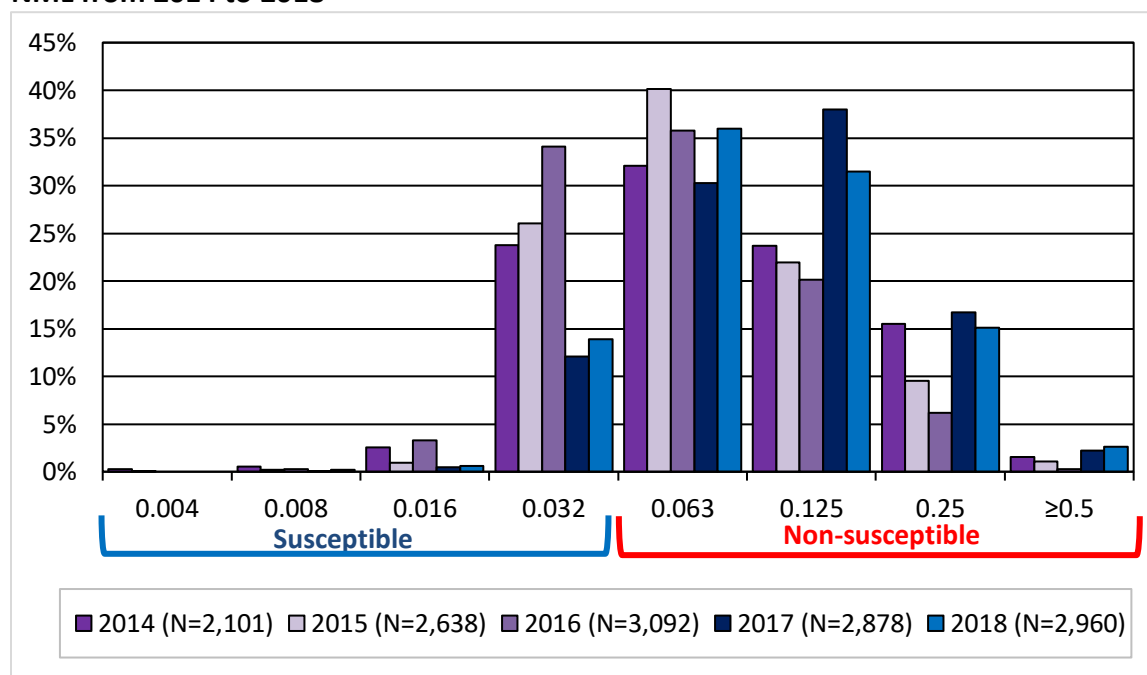
^aPercentage based on total number of isolates tested nationally: 2014=3,809; 2015=4,190; 2016=4,538; 2017=5,290; 2018=5,607

ERTAPENEM

The NML began testing ertapenem late in 2012. From 2014 to 2016, the ertapenem modal MIC was 0.063 mg/L. In 2017, the modal MIC increased to 0.125 mg/L but decreased back to 0.063 mg/L in 2018 (Figure 15).

Although there are no official MIC interpretative standards for *N. gonorrhoeae* for ertapenem, Unemo (2009) suggests that an ertapenem MIC of 0.032 mg/L is susceptible (S), and ertapenem MICs ≥ 0.064 mg/L are not susceptible (NS).

Figure 15. Trends of Ertapenem Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a



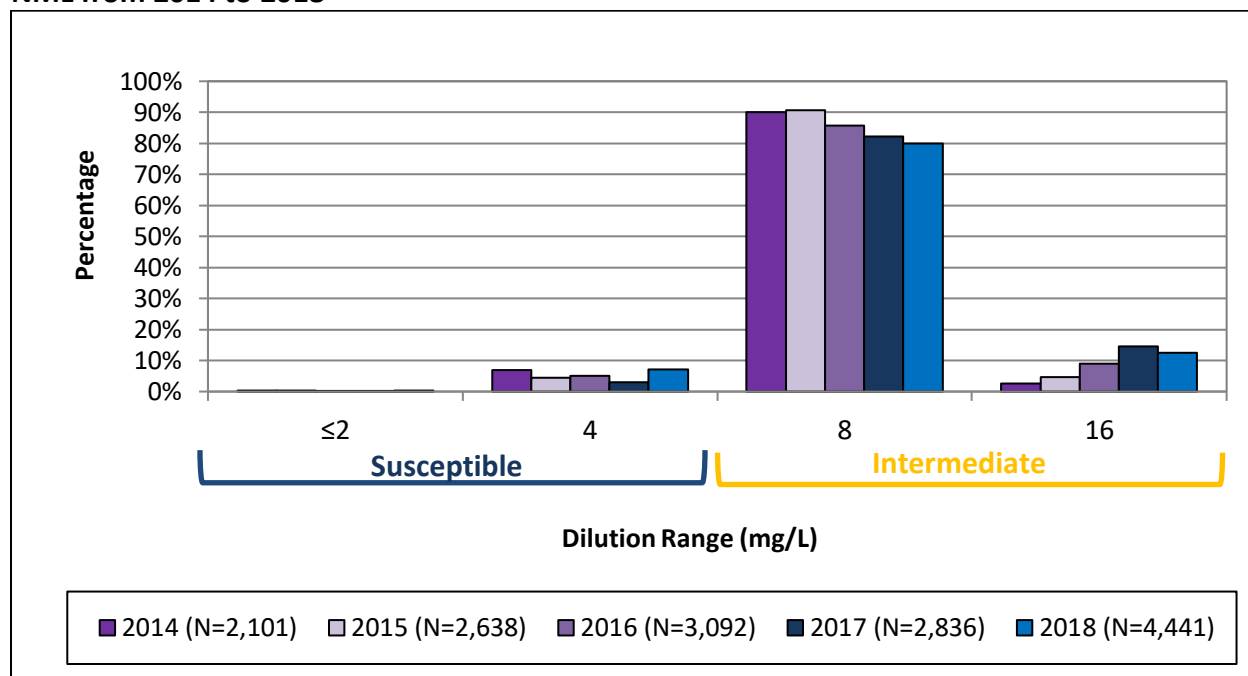
^aPercentages were calculated using the total number of viable strains (both resistant and susceptible isolates) tested by NML as the denominator (N).

GENTAMICIN

The NML began testing gentamicin late in 2012. The gentamicin modal MIC for all isolates tested from 2014 to 2018 is 8 mg/L (Figure 16).

Although there are no official MIC interpretative standards for *N. gonorrhoeae* gentamicin, Brown (2010) used the following criteria for gentamicin: R \geq 32 mg/L, I from 8 to 16 mg/L and S \leq 4 mg/L based on the Daly (1997) study.

Figure 16. Trends of Gentamicin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2014 to 2018^a



^aPercentages were calculated using the total number of viable strains (both resistant and susceptible isolates) tested by NML as the denominator (N).

NEISSERIA GONORRHOEAE MULTI-ANTIGEN SEQUENCING (NG-MAST)

NG-MAST molecular-based sequence typing provides a substantial level of discrimination between isolates. In 2018, the most common sequence types (STs) identified by the NML were ST-12302 (18.2%, 615/3,375), ST-14994 (16.6%, 562/3,375) and ST-5985 (5.8%, 195/3,375) (Figure 17).

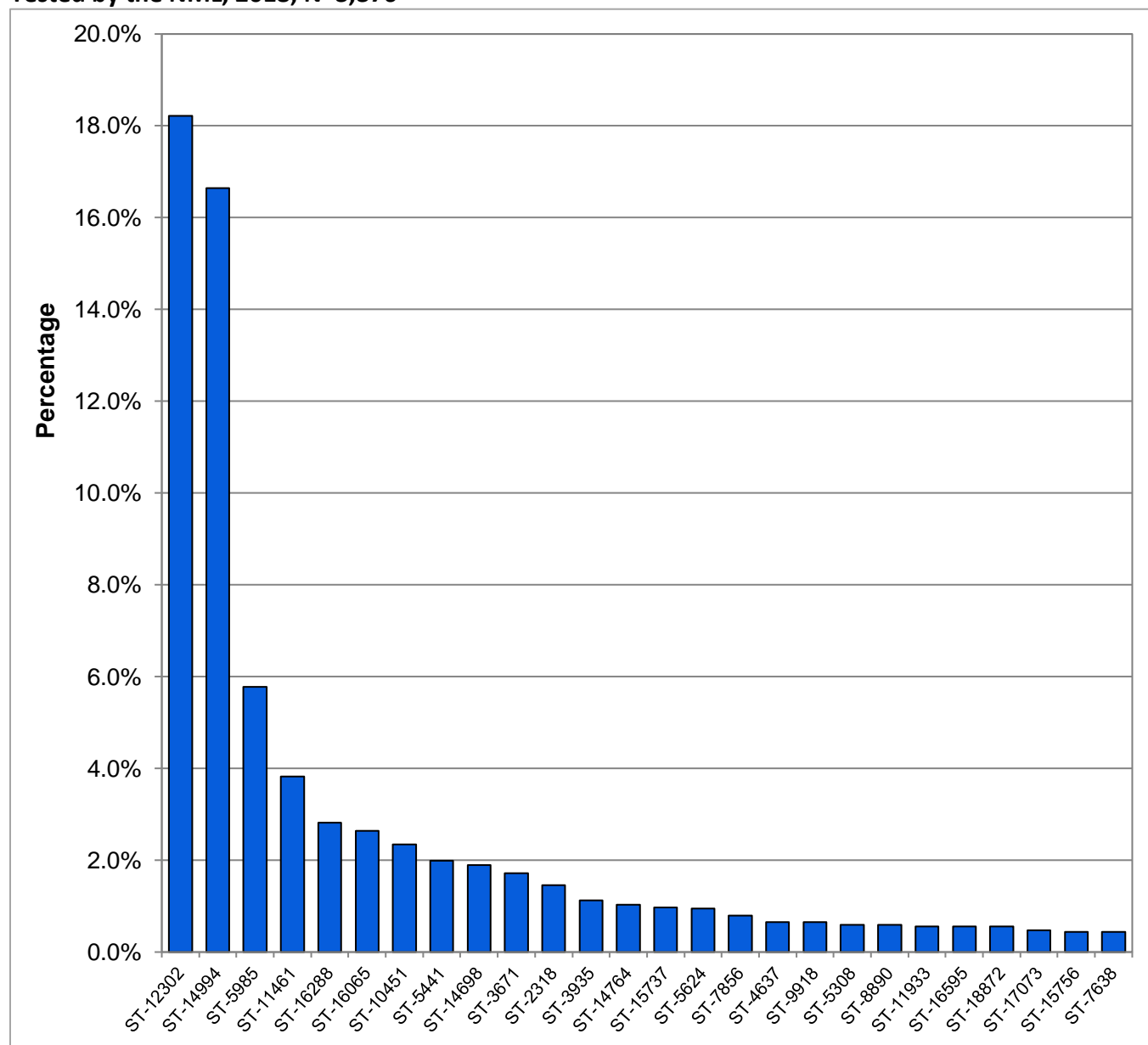
The proportion of ST-12302 isolates increased between 2015 (4.3%) and 2017 (24.1%) but decreased slightly in 2018 (18.2%) (Figure 18). ST-12302 isolates have primarily been identified in Quebec (n=324) and Ontario (n=217) but have also been found in British Columbia (n=32), Alberta (n=28), and Nova Scotia (n=12) (Figure 19). Canadian isolates identified in 2018 that are highly related to ST-12302 (Figure 23) include ST-14698 (n=64), ST-3935 (n=38), ST-17283 (n=14), ST-17380 (n=8) plus 40 other STs with one to seven isolates in each for a total of 940 which is 27.9% of all isolates typed in 2018. Isolates of this genogroup are resistant to multiple drugs with over 30% also resistant to azithromycin. The azithromycin MICs of these STs are primarily 1 or 2 mg/L. There are no isolates with decreased susceptibility to cefixime or ceftriaxone in this genogroup (Figure 21).

ST-14994 was newly identified in 2017 (2.1% (60/2,875) and increased to 16.6% (562/3,375) in 2018 (Figure 18). It was primarily identified in Ontario (n=288) and Quebec (n=237) with some found in Alberta (n=14), Manitoba (n=11) and British Columbia (n=9) (Figure 19). Canadian isolates identified in 2018 that have ≤ 5 base pair difference compared to ST-14994 include ST-15756 (n=15), ST-5785 (n=6), ST-16286 (n=3), ST-18995 (n=2) plus 2 other STs each with one isolate each for a total of 590 or 17.5% of isolates typed in 2018. These isolates are resistant to ciprofloxacin as well as various drugs with approximately 4% of them having resistance to azithromycin as well.

ST-5985 decreased from 11.9% in 2016 to 7.5% in 2017 and 5.8% in 2018 (Figure 18). These isolates are distributed through mostly western Canada: Alberta (n=113), Saskatchewan (n=44), Manitoba (n=16), Ontario (n=13), British Columbia (n=7) and Quebec (n=2) (Figure 19). In 2018, 6.5% (219/3,376) of Canadian isolates belong to the ST-5985 genogroup and include these highly related sequence types: ST-7440 (n=4), ST-14518 (n=2), ST-15125 (n=2), ST-15246 (n=2), ST-17365 (n=2), ST-118384 (n=2), ST-19532 (n=2) plus 8 other single ST types. Isolates of this genogroup are primarily TRNGs (94.5%,).

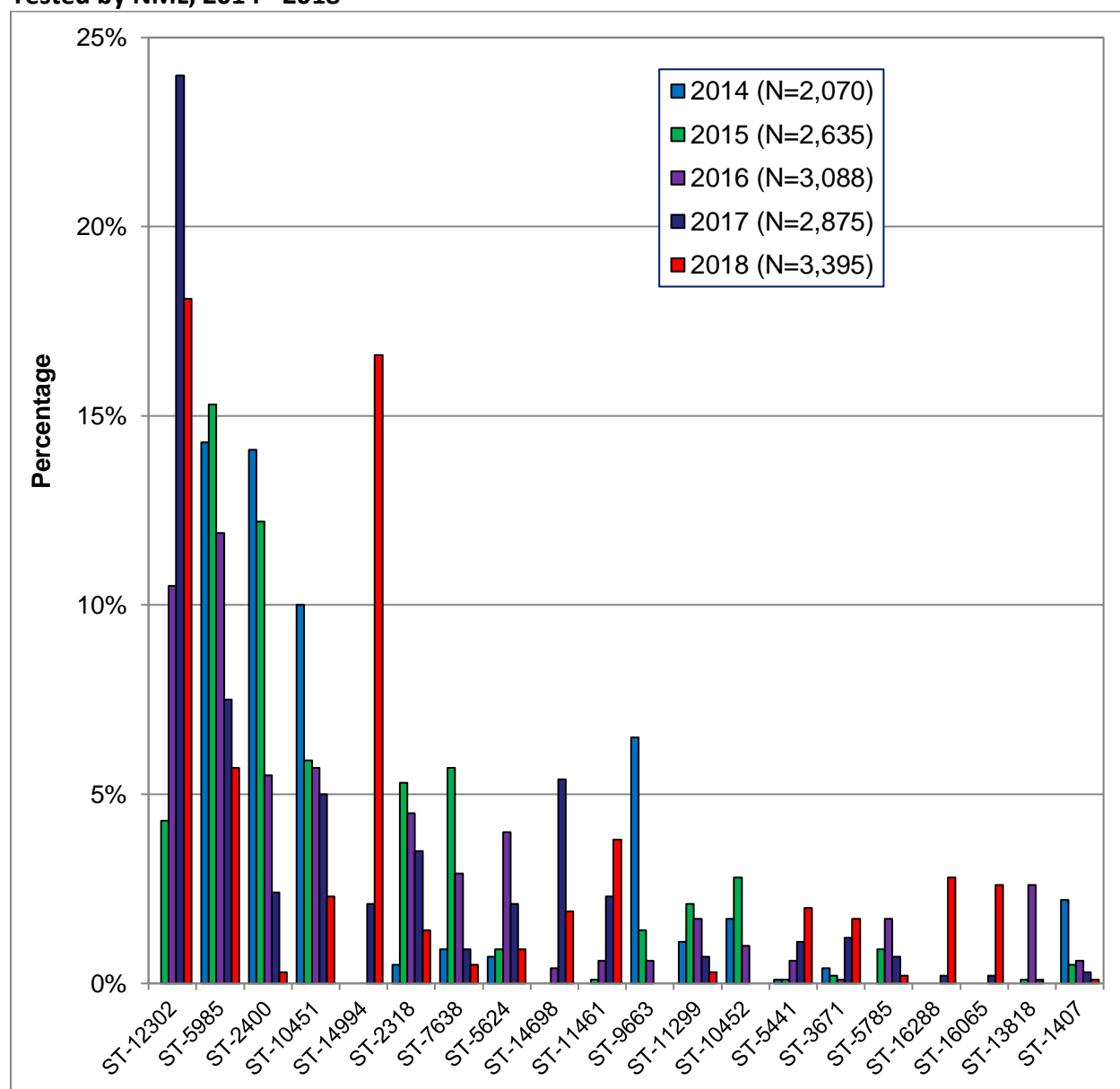
Distribution of STs within provinces is represented in Figure 20.

Figure 17. Prevalent NG-MAST Sequence Type Distribution of *Neisseria gonorrhoeae* Isolates Tested by the NML, 2018; N=3,376^a



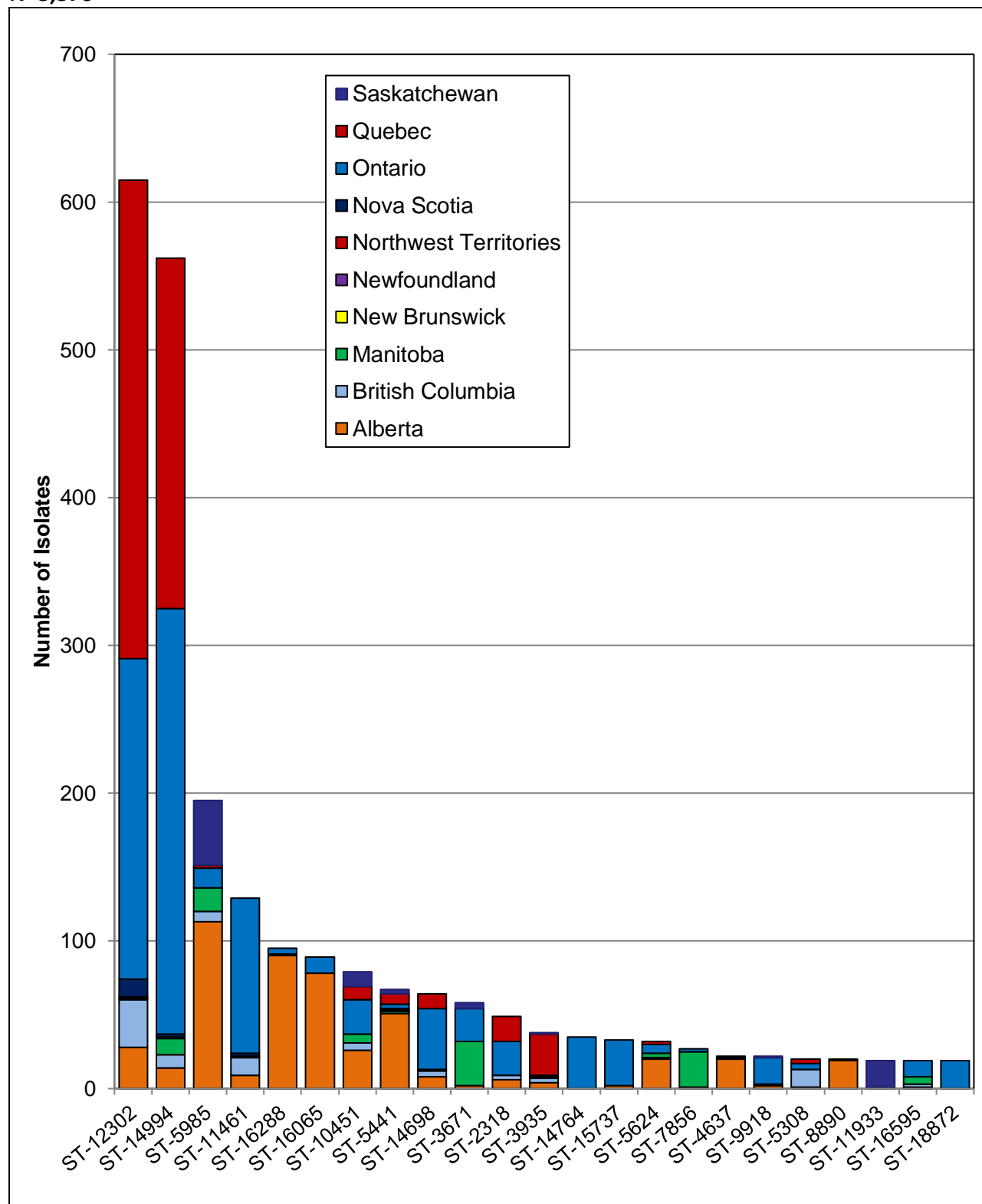
^a Does not include 21 isolates that were nontypeable. This graph represents 2,354 isolates. The remaining 1,022 isolates are dispersed among 477 sequence types (STs) containing 1 to 14 isolates each.

Figure 18. Trends of Prevalent NG-MAST Sequence Types of *Neisseria gonorrhoeae* Isolates Tested by NML, 2014 - 2018^a



^aA total of 378 sequence types were identified in 2014, 396 sequence types in 2015, 490 sequence types in 2016, 468 sequence types in 2017 and 503 in 2018. Only the most prevalent sequence types of 2014 to 2018 are represented in this graph.

Figure 19. Provincial Distribution within *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2018; N=3,376^a



^a Does not include 21 isolates that were nontypeable. This graph represents 2,308 isolates. The remaining 1,068 isolates are dispersed among 480 sequence types (STs).

Figure 20. Distribution of *Neisseria gonorrhoeae* NG-MAST Sequence Types within Provinces, 2018; N=3,376^a

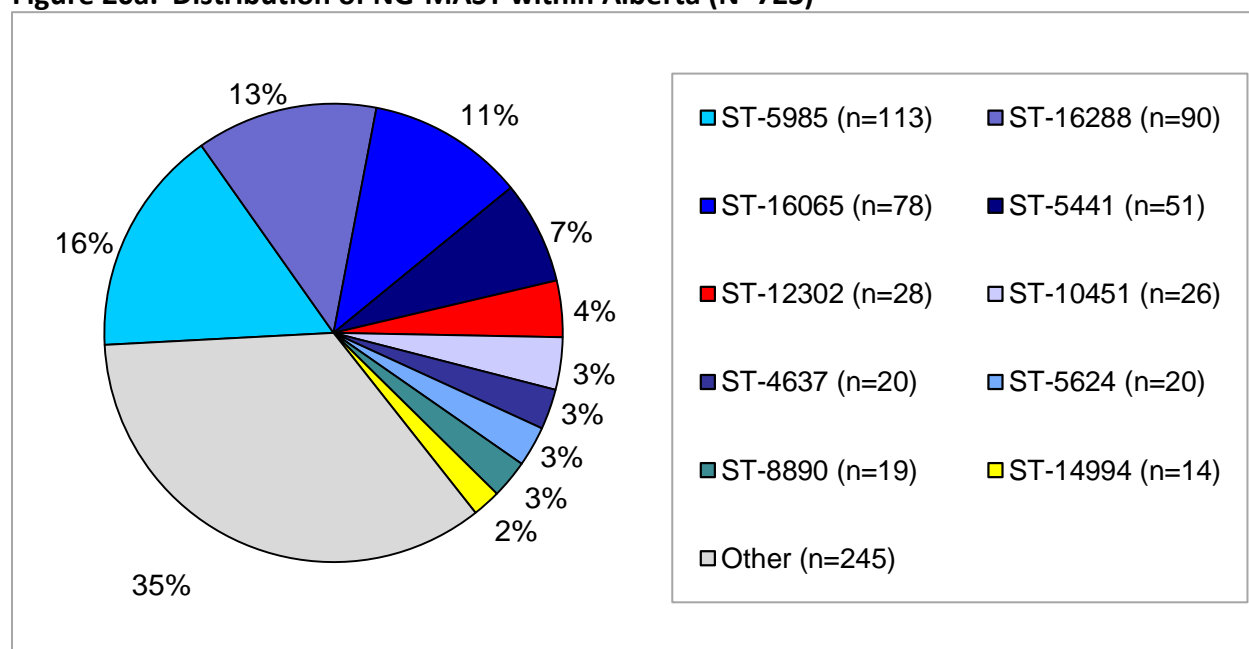
^a**New Brunswick (N=10):** ST-12302 (n=1), ST-14994 (n=1), ST-5441 (n=1), ST-1773 (n=1), ST-14917 (n=2), ST-16989 (n=1), ST-18258 (n=1), ST-18388, (n=1), ST-18402 (n=1)

Nova Scotia (N=31): ST-12302 (n=12), ST-14994 (n=2), ST-11461 (n=2), ST-16390 (n=2), ST-4224 (n=2) plus 11 other STs with a single isolate in each.

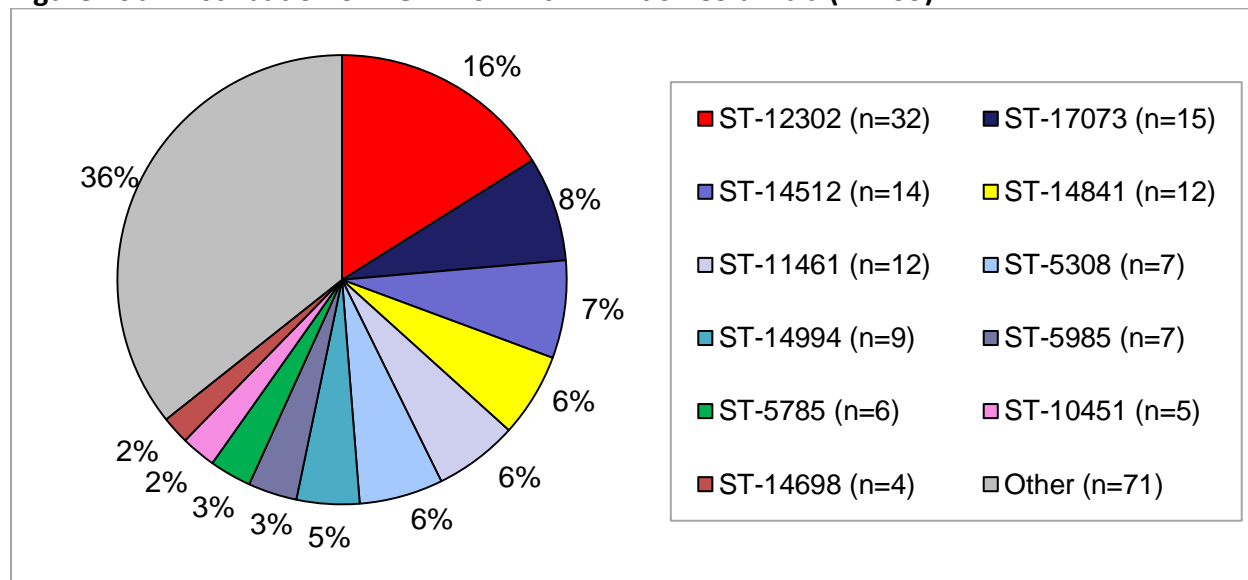
Newfoundland & Labrador (N=1): ST-12302 (n=1)

Northwest Territories (N=5): ST-14788 (n=2), ST-11461 (n=1), ST-5441 (n=1), ST-16958 (n=1)

Figure 20a. Distribution of NG-MAST within Alberta (N=723)^b



^bdoes not include 3 isolates that were nontypeable and the 168 isolates with submitted MIC data only

Figure 20b. Distribution of NG-MAST within British Columbia (N=199)^c

^cdoes not include 3 isolates that were nontypeable and the 290 isolates with submitted MIC data only

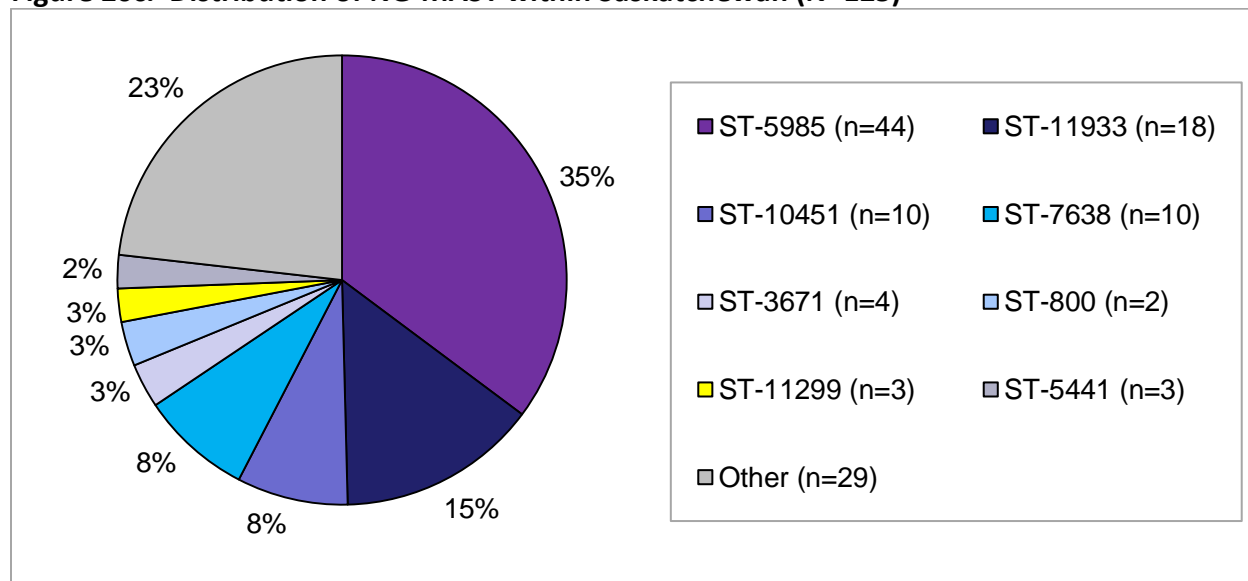
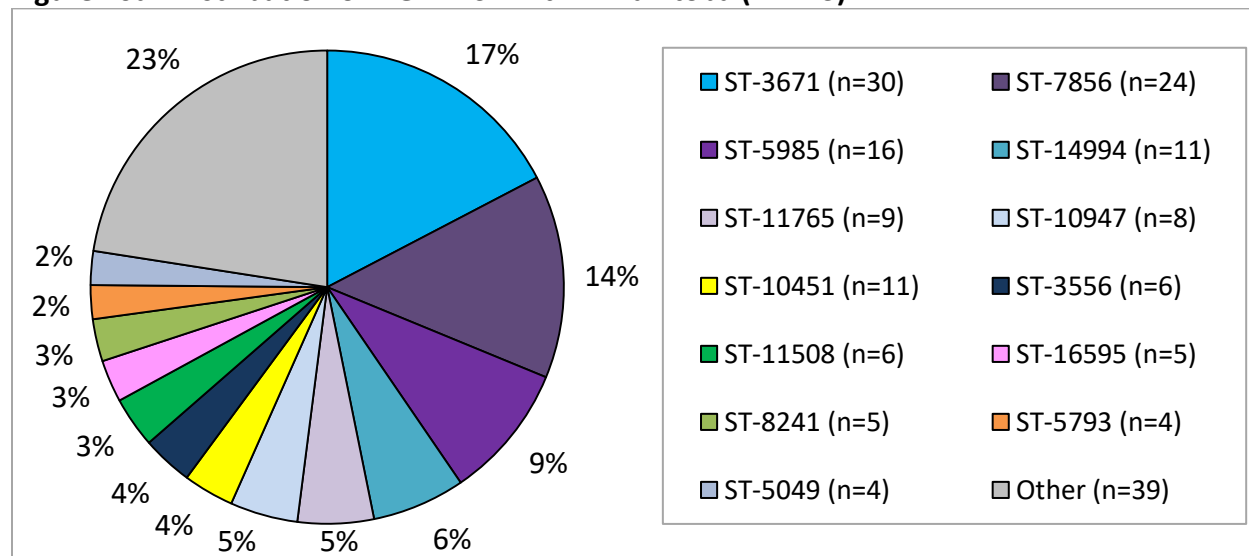
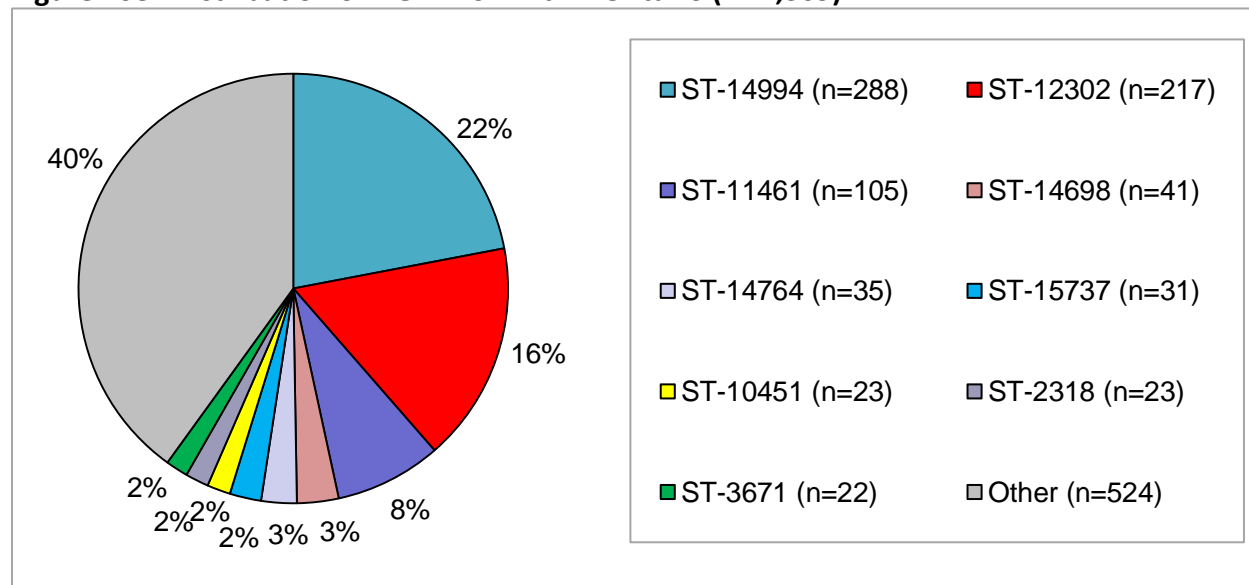
Figure 20c. Distribution of NG-MAST within Saskatchewan (N=125)

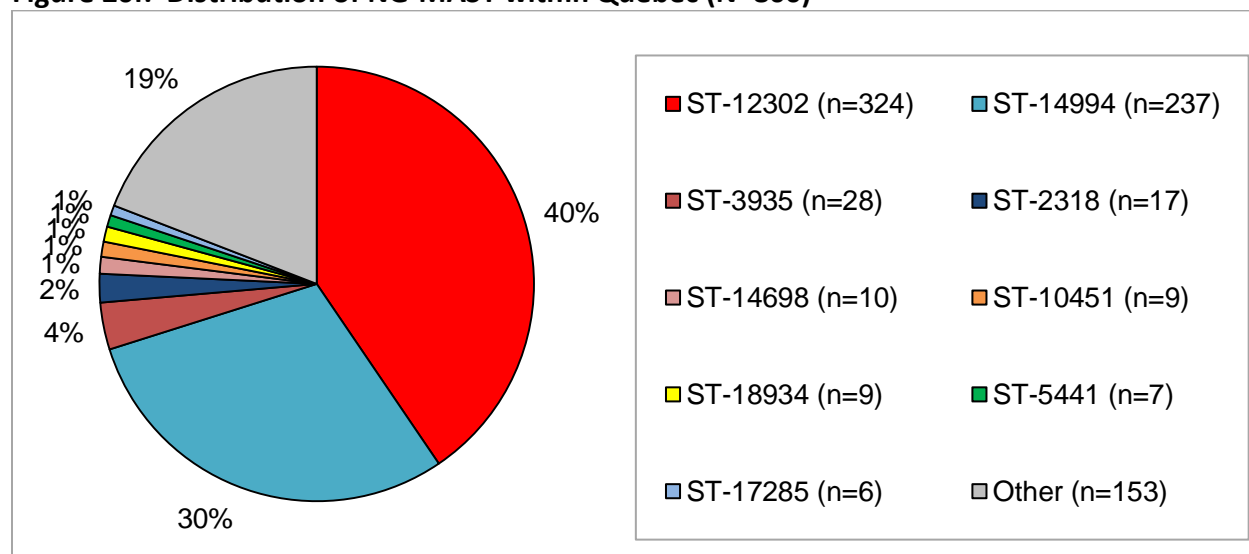
Figure 20d. Distribution of NG-MAST within Manitoba (N=173)^d

^ddoes not include 3 isolates that were nontypeable

Figure 20e. Distribution of NG-MAST within Ontario (N=1,309)^e

^edoes not include 10 isolates that were nontypeable

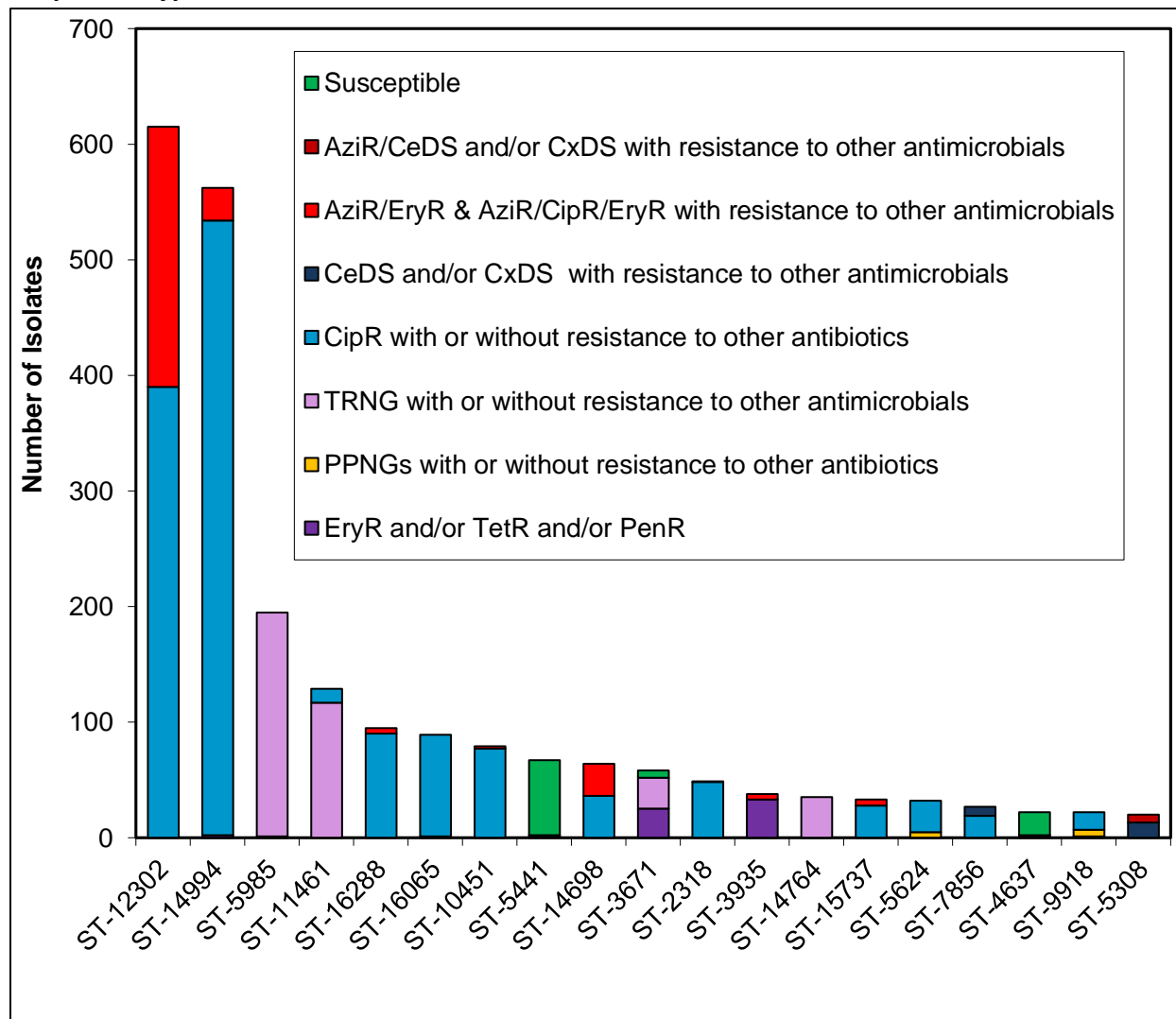
STs represented by different shades of red are all highly related to ST-12302 (differ by ≤ 2 base pairs)

Figure 20f. Distribution of NG-MAST within Quebec (N=800)^f

^f does not include 1,059 submitted isolates with MIC data only

STs represented by different shades of red are all highly related to ST-12302 (differ by ≤ 2 base pairs)

Figure 21. Distribution of Resistance Characterizations within *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2018; N=3,376^a



^a Does not include 21 isolates that were nontypeable. This graph represents 2,231 isolates. The remaining 1,145 isolates are dispersed among 483 sequence types (STs) containing 1 to 20 isolates each.

Figure 22 outlines the NG-MAST sequence types of isolates with decreased susceptibility to cefixime (Figure 22a), decreased susceptibility to ceftriaxone (Figure 22b), azithromycin resistant isolates (Figure 22c) and susceptible isolates (Figure 22d).

The most prevalent ST of isolates with decreased susceptibility to cefixime in 2018 was ST-5308 [74.1% (20/27)] followed by ST-18042 [7.4% (2/28)] (Figure 22a). ST-12016 (n=1), ST-16337 (n=1) and ST-18265 (n=1) are highly related (STs differ by ≤ 2 base pairs) to ST-5308 representing 85% (23/27) of isolates with decreased susceptibility to cefixime. Many of the isolates with decreased susceptibility to cefixime also had decreased susceptibility to ceftriaxone [77.8% (21/27)].

Isolates with decreased susceptibility to ceftriaxone were primarily ST-5308 [54.8% (17/31)] and ST-7856 [25.8% (8/31)] (Figure 22b). ST-5308 and ST-12016 (n=1) are highly related (differing by ≤ 2 base pairs) representing 58.1% (18/31) of isolates with decreased susceptibility to ceftriaxone. Many of the isolates with decreased susceptibility ceftriaxone also had decreased susceptibility to cefixime [67.7% (21/31)].

The ST types identified among the AziR isolates are displayed in Figure 22c. ST-12302 [52.7% (225/427)] is highly related (differ by ≤ 5 base pairs) to ST-14698 (n=28), ST-17283 (n=6), ST-3935 (n=5), ST-17380 (n=5) plus 39 other STs that contain azithromycin resistance. In total, the ST-12302 cluster is responsible for 79.6% (340/427) of the 2018 azithromycin resistant isolates that have STs identified.

The most prevalent STs of the susceptible isolates available for testing were ST-5441 [31.6% (65/206)] and ST-4637 [9.7% (20/206)] (Figure 22d). In addition, there are 7 STs, not included in the figure, that differ from ST-5441 by ≤ 4 base pairs making a total of 74 susceptible isolates in this cluster. Note that the majority of susceptible isolates were not submitted to the NML and therefore do not have sequence types identified.

Figure 22. NG-MAST Sequence Types of 2018 *Neisseria gonorrhoeae* Isolates^a

Figure 22a. Decreased Susceptibility to Cefixime (MIC ≥ 0.25 mg/L), N=27^a

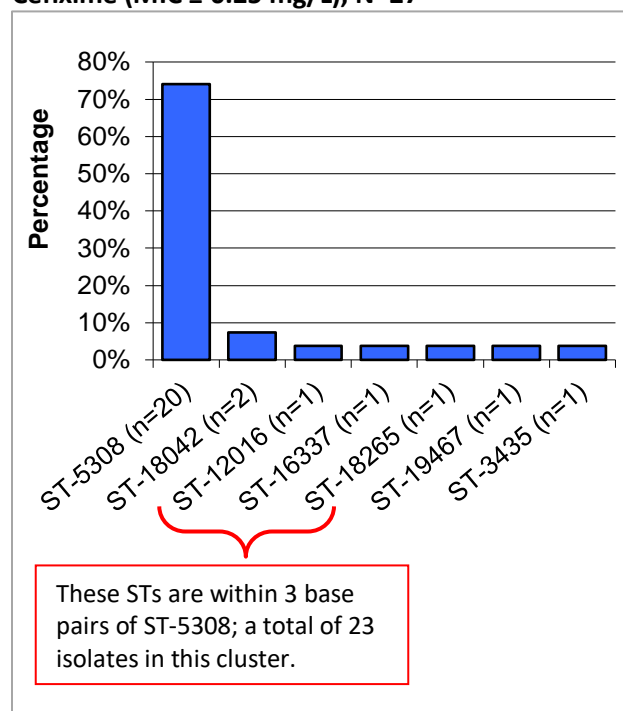


Figure 22b. Decreased Susceptibility to Ceftriaxone (MIC ≥ 0.125 mg/L), N=31

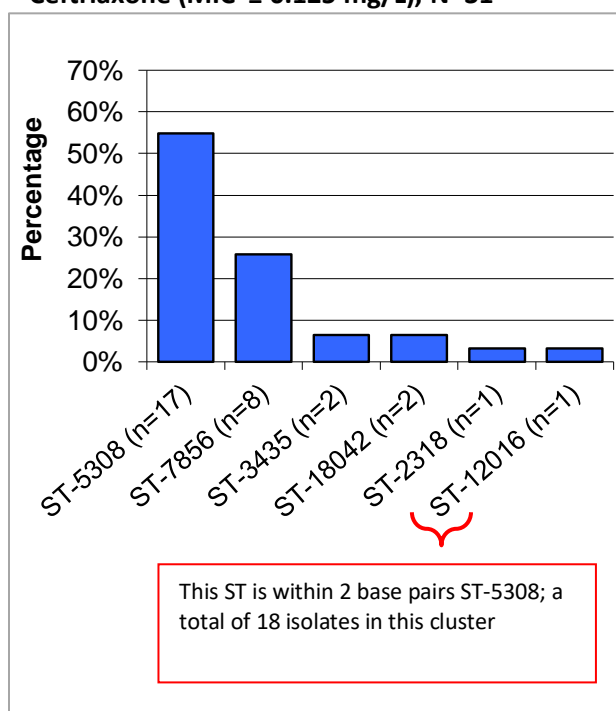


Figure 22c. Azithromycin Resistant (MIC ≥ 2 mg/L), N=427^a

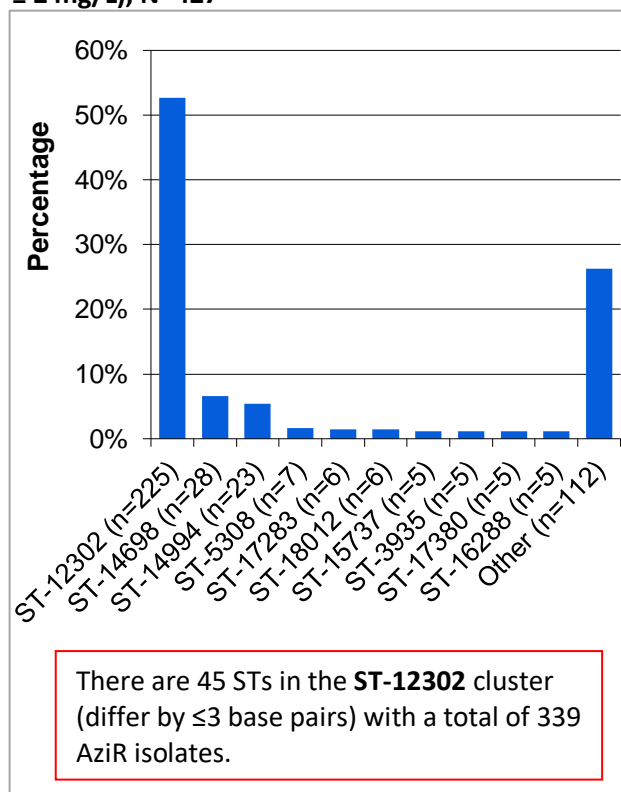
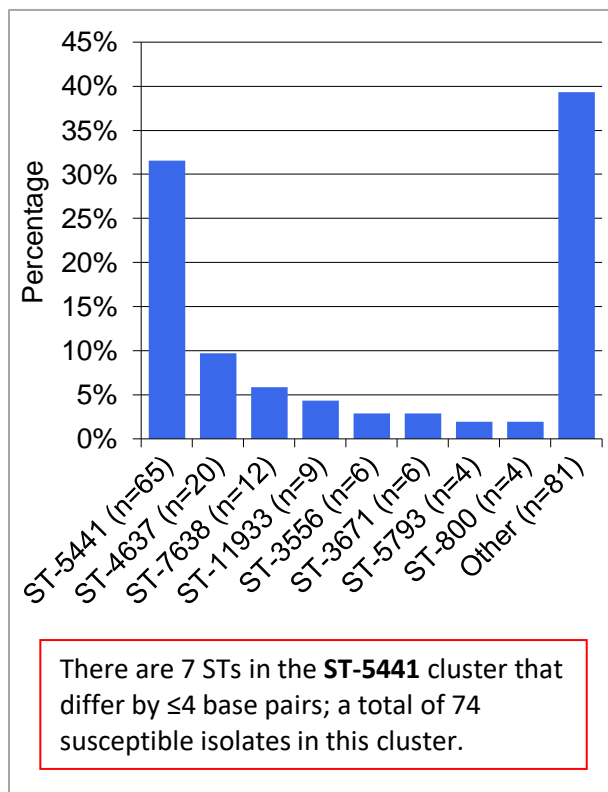


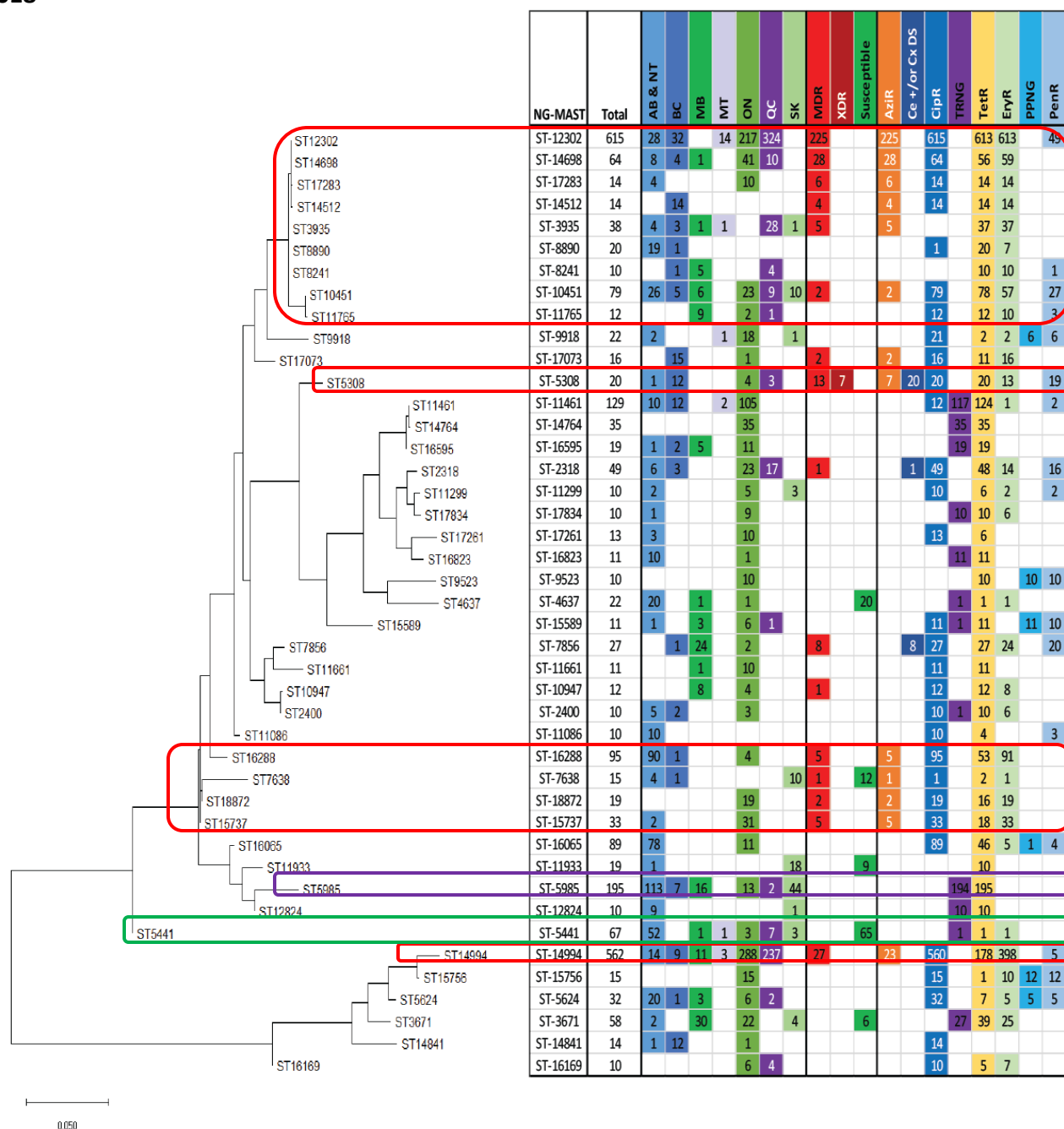
Figure 22d. Susceptible Isolates, N=206^{bc}



^a Does not include 1 isolate that were nontypeable. Other sequence types of azithromycin resistant isolates contain 1 to 4 isolates each

^b Susceptible isolates are isolates that were tested at the NML and not resistant to any of the antibiotics tested. Does not include 3 nontypeable isolates.

^c Other sequence types of susceptible isolates contain 1 to 3 isolates each.

Figure 23. Genetic Relationship of Prevalent *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2018^{ab}

^{ab}This tree represents the 43 most prevalent STs of 2018 with 2,546 isolates. The remaining 830 isolates are dispersed among 460 STs containing 1 to 9 isolates each.

^bbp=nucleotide base pair

The evolutionary history was inferred by using the Maximum Likelihood method based on the Jukes-Cantor model [1]. The tree with the highest log likelihood (-5321.99) is shown. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 43 nucleotide sequences. Codon positions included were 1st+2nd+3rd+Noncoding. All positions containing gaps and missing data were eliminated. There were a total of 804 positions in the final dataset. Evolutionary analyses were conducted in MEGA X [2].

CONCLUSION

N. gonorrhoeae is the most commonly reported antimicrobial-resistant sexually transmitted infection. The evolution of antimicrobial resistance in gonorrhea is complex and efficient. The emergence and spread of resistant isolates is a recognized global public health threat. It is important to monitor changes in the characteristics and prevalence of the resistant isolate populations and their spread across the country in order to guide therapeutic recommendations. Additionally, the regional, provincial/territorial and federal public health departments can use the national antimicrobial susceptibility surveillance data to identify novel resistance, set research priorities, assess and allocate gonorrhea prevention services and resources, guide gonorrhea resistance control planning and ensure health care providers have access to and follow current best practices in diagnosis and treatment recommendations.

Reports of cefixime treatment failures and the observed MIC creep between 2001 and 2011 for both cefixime (from 0.016 mg/L to 0.125 mg/L) and ceftriaxone (from 0.016 mg/L to 0.063 mg/L) led to changes in gonorrhea treatment approaches. In 2012, the Canadian STI Guidelines issued updated recommendations for the use of combination gonorrhea therapy with 250 mg ceftriaxone intramuscularly and azithromycin 1 g orally as the first-line regimen in men who have sex with men (MSM) and in pharyngeal infections (Public Health Agency of Canada, 2016). The United States (CDC, 2012) and Europe (Bignell, 2013) also updated treatment recommendations to combination therapy with intramuscular ceftriaxone and oral azithromycin. Since the 2012 changes to Canadian gonorrhea treatment recommendations there has been a decrease in the proportion of isolates with elevated MICs to the cephalosporins. According to the WHO definition (decreased susceptibility MIC \geq 0.25 mg/L for cefixime and \geq 0.125 mg/L for ceftriaxone), decreased susceptibility to cefixime declined from 2.2% (68/3,036) in 2012 to 0.5% (27/5,607) in 2018. Decreased susceptibility to ceftriaxone also declined from 5.5% (168/3,036) in 2012 to 0.6% (31/5,607) in 2018.

Similarly, the US reported a decline in decreased susceptibility to cefixime from 1.4% in 2011 to 0.3% in 2018. Decreased susceptibility to ceftriaxone declined from 0.4% in 2011 to 0.2% in 2018 (CDC, 2018). The UK reported that the prevalence of isolates with decreased cefixime susceptibility dropped from 1.3% in 2011 to 0.4% in 2015 but has since increased to 2.2% in 2018. Decreased susceptibility to ceftriaxone remained at 0% from 2011 to 2018 (Public Health England, 2018). Using 0.06 mg/L as the decreased susceptibility breakpoint, Australia reported 1.1% decreased susceptibility to ceftriaxone in 2017 which had decreased from 8.8% in 2013 (Lahra, 2017). Only 0.04% of isolates in Australia had ceftriaxone MICs of 0.125 mg/L in 2017, but there were two isolates with MICs of 0.5 mg/L (Lahra, 2017).

The decline in decreased susceptibility to cephalosporins is encouraging, however, in 2017, routine surveillance confirmed the first ceftriaxone resistant (MIC=1 mg/L) *N. gonorrhoeae* in Canada (Lefebvre, 2018). This isolate was identified in an asymptomatic female whose partner had travelled to China and Thailand. The strain was resistant to ceftriaxone, cefixime, ciprofloxacin and tetracycline, but was susceptible to azithromycin. The case was treated successfully using cefixime and azithromycin. Whole genome sequencing revealed that the isolate was genetically linked to *N.gonorrhoeae* isolate FC428 that was first identified in Japan and now identified in other countries through travel (Lahra, 2018). In 2018, a second ceftriaxone resistant (MIC = 0.5 mg/L) isolate was identified in Canada. This case was identified in Alberta and was related to travel to South East Asia. This isolate was also resistant to cefixime (MIC = 2 mg/L), ciprofloxacin, erythromycin, penicillin and tetracycline but was susceptible to azithromycin. This case was

initially treated with combination ceftriaxone and azithromycin treatment but the infection recurred and he was successfully treated with 240 mg of IM gentamicin and a single 2 g oral dose of azithromycin (Smyczek, 2019, Berenger, 2019). The NG-MAST (ST-3435), NG-STAR (233) and MLST (1903) were identical to FC428 and whole genome sequencing showed a genetic relatedness. In Ontario, two additional ceftriaxone resistant *N. gonorrhoeae* were identified in patients that were sexual partners also with travel history to South East Asia. Routine antimicrobial susceptibility surveillance programs will ensure isolates such as these are rapidly recognized so that contact tracing and public health intervention methods control the spread of these resistant isolates.

Azithromycin resistance continues to be of concern. In 2018, 7.6% of all isolates tested were azithromycin resistant. Over 90% of these isolates are resistant to other antimicrobials including ciprofloxacin, tetracycline and penicillin. While the proportion of azithromycin resistance has decreased from 11.7% in 2017, the number of isolates with an azithromycin MIC = 1 mg/L, which is just one dilution from the resistance breakpoint, has increased by over 50%. Since the acceptable range of error is +/- 1 doubling dilution for MICs, it is possible that our reported azithromycin resistance rate is much higher than 7.6%. In Canada, the level of azithromycin resistance levels exceeded that in the US, which was reported as 4.6% in 2018 (CDC, 2018). Australia reported an increase in azithromycin resistance from 2.1% in 2013 to 9.3% in 2017 (Lahra, 2017). The UK reported an increase in azithromycin resistance (MIC \geq 1 mg/L) from 1.0% in 2014 to 9.7% in 2018 (Public Health England, 2018) and recently updated their recommended gonococcal treatment to monotherapy 1 g ceftriaxone IM single dose (Fifer, 2019).

In 2018, seven isolates with resistance to azithromycin and decreased susceptibility to cefixime and ceftriaxone (XDR-GC) were identified (BC n=5, QC n=2). All of these isolates were ST-5308. Both the US and Australia did not identify any isolates with this antimicrobial profile (CDC, 2018, Lahra, 2017). The UK, however, reported 3 XDR-GC in 2018, all related to travel (Public Health England, 2018).

Enhancing surveillance to include linked epidemiological and laboratory data would address the limitations regarding data representativeness and interpretation in the current passive surveillance system. The Enhanced Surveillance of Antimicrobial Resistant Gonorrhea (ESAG) was initiated in 2014 and is being assessed to fill this gap.

It is imperative that surveillance and monitoring of the antimicrobial susceptibilities and sequence types of *N. gonorrhoeae* continue to inform and subsequently mitigate the impact of antimicrobial resistance in gonorrhea. These gonococcal surveillance data will be utilized in the future iterations of the Canadian STI guidelines to provide information on the most effective treatment of *N. gonorrhoeae* and to reduce the prevalence and spread of drug resistant gonorrhea.

APPENDIX A

***Neisseria gonorrhoeae* culture isolates in Canada, 2014 – 2018^a**

Province/ Territory	2014 GC Cultures			2015 GC Cultures			2016 GC Cultures			2017 GC Cultures			2018 GC Cultures		
	Tested in each province	Received at NML ^b	% Sent to NML for Testing	Tested in each province	Received at NML ^b	% Sent to NML for Testing	Tested in each province	Received at NML ^b	% Sent to NML for Testing	Tested in each province	Received at NML ^b	% Sent to NML for Testing	Tested in each province	Received at NML ^b	% Sent to NML for Testing
British Columbia	492	336	68.3%	602	387	64.3%	600	348	58.0%	478	292	61.1%	489	219	44.8%
Alberta	468	339	72.4%	793	514	64.8%	786	544	69.2%	895	762	85.1%	899	838	93.2%
Saskatchewan	91	91	100.0%	62	64	100.0%	86	85	99.0%	133	120	90.2%	132	134	100%
Manitoba	46	46	100.0%	48	45	93.7%	85	82	96.5%	134	130	97.0%	183	196	100%
Ontario	1,767	855	48.4%	1,673	1,075	64.3%	1,735	1,068	61.6%	2,108	1,305	61.9%	1,981	1370	69.2%
Québec	918	408	44.4%	986	528	53.5%	1,197	927	77.4%	1,486	1,486	100.0%	1,874	805	43.0%
Nova Scotia	15	14	93.3%	13	15	100.0%	32	31	97.0%	29	29	100.0%	31	35	100%
Other ^c	12	12	100.0%	13	11	84.6%	17	7	41.2%	27	19	70.7%	18	19	100%
Totals	3,809	2,101	55.2%	4,190	2,639	63.0%	4,538	3,092	68.1%	5,290	3,092	58.4%	5,607	3,616	64.5%

^aNo *Neisseria gonorrhoeae* cultures were reported to the NML or received from Nunavut or the Yukon in 2014 to 2018.

^bNot including duplicates or isolates that were contaminated or did not grow for the NML.

^cOther includes New Brunswick, Newfoundland, Prince Edward Island and Northwest Territories

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