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National Surveillance of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Annual Summary 2016

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 Infection Control
Public Health Agency of Canada

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Neisseria gonorrhoeae cultures were not reported to the NML or received from Nunavut or the Yukon.

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EXECUTIVE SUMMARY

- This report compares laboratory surveillance data for *Neisseria gonorrhoeae* isolates submitted by provincial microbiology laboratories to the National Microbiology Laboratory (NML) from 2012 - 2016.
- The Canadian reported rate of gonorrhea is on the rise and has more than doubled from 21.8 per 100,000 in 2001 to 55.4 per 100,000 in 2015. Gonorrhea is the second most commonly reported bacterial sexually transmitted infection in Canada with 19,845 cases reported in 2015.
- 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 2016, a total of 4,538 *N. gonorrhoeae* isolates were cultured and tested in public health laboratories across Canada; 3,092 of these were submitted to the NML for antimicrobial susceptibility testing. The total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportion.
- The following WHO breakpoints were used throughout this report: decreased susceptibility to cefixime at MIC≥0.25 mg/L and decreased susceptibility to ceftriaxone at MIC≥0.125 mg/L (WHO, 2012).
- Isolates with decreased susceptibility to cefixime have declined from 1.9% (80/4,190) in 2015 to 0.3% (14/4,538) in 2016.
- Isolates with decreased susceptibility to ceftriaxone declined from 3.5% (146/4,190) in 2015 to 1.8% (80/4,538) in 2016.
- The proportion of azithromycin resistant (MIC≥2 mg/L) *N. gonorrhoeae* isolates increased steadily from 0.9% (26/3,036) in 2012 to 4.7% (198/4,190) in 2015. In 2016, 7.2% (326/4,538) of isolates tested were resistant to azithromycin.
- In 2016, 47.1% (2,136/4,538) of isolates were resistant to ciprofloxacin; 31.7% (1,439/4,538) of the isolates were resistant to erythromycin; 17.4% (791/4,538) were resistant to penicillin; and 53.3% (2,419/4,538) were resistant to tetracycline.
- All *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 2016, 490 different sequence types (STs) were identified among the 3,092 isolates tested and the most common sequence types were ST-5985 (11.9%), ST-12302 (10.5%) and ST-10451 (5.7%).
- ST-12302 increased from 4.3% of all isolates in 2015 to 10.5% in 2016; the isolates were primarily identified in central Canada. ST-12302 isolates were resistant to multiple drugs with over 70% also resistant to azithromycin.

- ST-10451 is highly related to ST-1407, an internationally identified clone that has been described as a superbug, with high-level resistance to cephalosporins. Most ST-10451 isolates identified in 2016 were resistant to multiple drugs and over 5% of these were resistant to azithromycin.
- In 2016, only 1 isolate with resistance to azithromycin and decreased susceptibility to cefixime and ceftriaxone was detected in Canada. It was identified as ST-2318.

INTRODUCTION

Neisseria gonorrhoeae is the causative agent of gonorrhoea and is the second most commonly reported bacterial sexually transmitted infection in Canada, with 19,845 cases reported in 2015 (Public Health Agency of Canada, 2017). Rates of reported cases of gonorrhea have increased from 21.8 cases per 100,000 population in 2001 to 55.4 cases per 100,000 population in 2015 (Public Health Agency of Canada, 2017). 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, 2013). 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 (Barry, 2009; Tapsall, 2006). 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. 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 (STI) updated gonorrhea treatment guidance to recommend combination therapy with 2 antibiotics. In pharyngeal infections and uncomplicated anogenital infections in men who have sex with men (MSM), 250 mg ceftriaxone intramuscularly and azithromycin 1 g orally first-line treatment is recommended. 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

A further 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 70% of gonococcal infections in Canada are now diagnosed using NAAT.

To make improvements to the current surveillance program, the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea (ESAG) was initiated in 2014. 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 antimicrobial susceptible and resistant strains of gonorrhea are characterized in order to understand the pattern of spread of strains in various populations in Canada and to inform Canadian guidance on STI management.

The National Microbiology Laboratory (NML), in collaboration with the provincial laboratories, has been monitoring the antimicrobial susceptibilities of *N. gonorrhoeae* since the mid 1970's; these results inform the gonococcal infection treatment recommendations in the Canadian Guidelines on Sexually Transmitted Infections.

METHODS

In 2016, provincial public health laboratories submitted a total of 3,092 viable *N. gonorrhoeae* isolates to the NML for antimicrobial susceptibility testing as part of the passive National *Neisseria gonorrhoeae* Surveillance Program. 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 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. The overall interpretation of the results is difficult due to the limitations related to the isolates available for testing. The total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportion. 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. Plasmid testing is no longer performed. *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, 2012 - 2016[ab]

Province[a]	2012	2013	2014	2015	2016	Total
British Columbia	92	170	375	408	370	1,415
Alberta	94	136	382	608	624	1,844
Saskatchewan	57	67	93	64	91	372
Manitoba	8	7	46	58	89	208
Ontario	403	498	893	1,139	1,119	4,052
Québec	390	301	432	549	930	2,602
New Brunswick	3	5	3	10	4	25
Nova Scotia	0	1	15	16	33	65
Newfoundland	0	1	9	1	0	11
Prince Edward Island	1	2	0	1	0	4
Northwest Territories	0	0	0	2	4	6
Total isolates received at NML	1,048	1,188	2,248	2,856	3,264	10,604
Total viable, non-duplicate isolates available for testing[b]	1,031	1,183	2,101	2,638	3,092	10,045
Total isolates resistant to at least one antibiotic	987	1,153	1,995	2,530	2,933	9,598
Total number of isolates tested in all provinces and territories[c]	3,036	3,195	3,809	4,190	4,538	18,768
Percentage of isolates resistant to at least one antibiotic	32.5%	36.1%	52.4%	60.4%	64.6%	51.1%
Percentage of total cases tested	24.2%	23.2%	23.4%	21.1%	22.9%	22.8%
Total cases reported in Canada	**12,561**	**13,786**	**16,285**	**19,845**	**19,845[d]**	**82,322 [d]**

[a]Nunavut and the Yukon did not report or send any *Neisseria gonorrhoeae* cultures to the NML from 2012 to 2016
[b]Isolates that were duplicates (from same patient and same collection date or treatment failures), contaminated or did not grow were excluded.
[c]Total number of isolates tested by the provincial laboratories is used as the denominator in all % resistance calculations.
[d]2016 total cases reported in Canada is estimated based on 2015 numbers.

Table 2. *Neisseria gonorrhoeae* Antimicrobial Resistance Criteria[ab]

Antibiotic	Recommended Testing Concentration Ranges (mg/L)	MIC Interpretive Standard (mg/L)				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	Bayer Health Care
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	MP Biomedicals

na=not applicable

[a]MIC Interpretative standards as recommended by the Clinical and Laboratory Standards Institute (CLSI M100, 2017) except for erythromycin (Ehret, 1996), azithromycin (Centres for Disease Control and Prevention, 2007) , ceftriaxone and cefixime (World Health Organization, 2012) , ertapenem (Unemo, 2009) and gentamicin (Brown, 2010 & Daly, 1997).

[b]S= Susceptible, I=Intermediate, R= Resistant, DS= Decreased susceptibility

Table 3. *Neisseria gonorrhoeae* Antimicrobial Resistance Characterization Definitions

Characterization	Definition	Description
PPNG	Penicillinase Producing *Neisseria gonorrhoeae*	Pen MIC ≥ 2.0 mg/L, β-lactamase positive
TRNG	Tetracycline Resistant *Neisseria gonorrhoeae*	Tet MIC ≥ 16.0 mg/L, TetM PCR positive
CMRNG	Chromosomal Mediated Resistant *Neisseria gonorrhoeae*	Pen MIC ≥ 2.0 mg/L, Tet MIC ≥ 2.0 mg/L but ≤ 8.0 mg/L, and Ery MIC ≥ 2.0 mg/L
Probable CMRNG	Probable Chromosomal Mediated Resistant *Neisseria gonorrhoeae*	One of the MIC values of Pen, Tet, Ery = 1 mg/L, the other two ≥ 2.0 mg/L
PenR	Penicillin Resistant *Neisseria gonorrhoeae*	Pen MIC ≥ 2.0 mg/L, β-lactamase negative
TetR	Tetracycline Resistant *Neisseria gonorrhoeae*	Tet MIC ≥ 2.0 mg/L but ≤ 8.0 mg/L
EryR	Erythromycin Resistant *Neisseria gonorrhoeae*	Ery MIC ≥ 2.0 mg/L
CipR	Ciprofloxacin Resistant *Neisseria gonorrhoeae*	Cip MIC ≥ 1.0 mg/L
AzR	Azithromycin Resistant *Neisseria gonorrhoeae*	Az MIC ≥ 2.0 mg/L
SpecR	Spectinomycin Resistant *Neisseria gonorrhoeae*	Spec MIC ≥ 128 mg/L
CxDS	*Neisseria gonorrhoeae* with Decreased Susceptibility to Ceftriaxone	Cx MIC ≥ 0.125 mg/L
CeDS	*Neisseria gonorrhoeae* with Decreased Susceptibility to Cefixime	Ce MIC ≥ 0.25 mg/L

RESULTS AND DISCUSSION

In 2016, a total of 4,538 *N. gonorrhoeae* isolates were cultured in public health laboratories across Canada; 3,092 of these were submitted to the NML and found viable for antimicrobial susceptibility testing. A total of 2,933 of submitted isolates were found to be resistant to at least one antibiotic tested representing an increase from 60.4% (2,530/4,190) in 2015 to 64.6% (2,933/4,538) in 2016 (Figure 1). Of all the gonorrhea cases reported in 2015, over 70% were diagnosed by NAAT for which there is no antimicrobial susceptibility data.

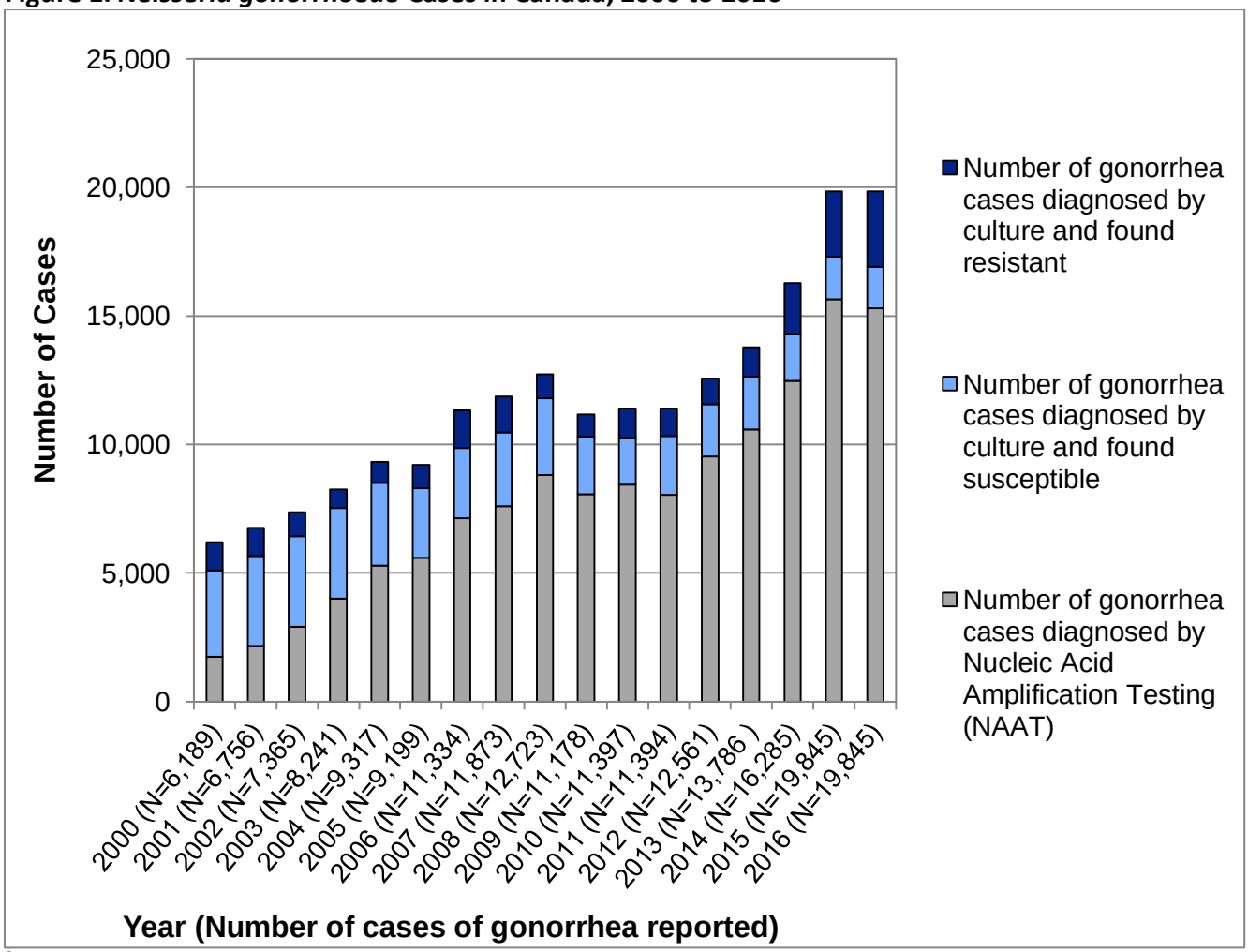
Gender and age data were available for 99.8% (3,085/3,092) of isolates tested at the NML (Table 4). Of these, 86.5% (2,674/3,092) were males ranging from infancy to 82 years of age. A total of 13.2% (407/3,092) of isolates were from females ranging from infancy to 68 years.

Anatomic source data was available for 99.9% (3,088/3,092) of the isolates sent to the NML (Table 4). Of these, 51.2% (1,582/3,092) were urethral, 22.7% (702/3,092) were rectal, 15.4% (475/3,092) were from the throat, 6.0% (185/3,092) were cervical, 2.1% (66/3,092) were vaginal, 0.8% were ocular (25/3,092) and 1.7% (53/3,092) were from other sources.

Table 4. Age of patient and isolation site of the *Neisseria gonorrhoeae* isolates tested at the NML, 2016 (N=3,092)

Patient characteristics	Male	Female	Not Given	Total
Age	no. (%)	no. (%)	no. (%)	no. (%)
Under 15	3 (0.1)	4 (0.1)	0 (0)	7 (0.2)
15 - 20	173 (5.6)	72 (2.3)	0 (0)	245 (7.9)
21 - 25	559 (18.1)	115 (3.7)	1 (0)	675 (21.8)
26 - 30	612 (19.8)	97 (3.1)	1 (0)	710 (23.0)
31 - 40	725 (23.4)	78 (2.5)	3 (0.1)	806 (26.1)
41 - 50	343 (11.1)	27 (0.9)	0 (0)	370 (12.0)
51 - 60	195 (6.3	11 (0.4)	1 (0)	207 (6.7)
60 +	62 (2.0	3 (0.1)	0 (0)	65 (2.1)
Not Specified	2 (0.1)	0 (0)	5 (0.2)	7 (0.2)
Total	2,674 (86.5)	407 (13.2)	11 (0.4)	3,092 (100)
Isolation Site				
Penis/ Urethra	1,574 (50.9)	3 (0.1)	5 (0.2)	1582 (51.2)
Rectum	660 (21.3)	38 (1.2)	4 (0.1)	702 (22.7)
Throat	379 (12.3)	94 (3)	2 (0.1)	475 (15.4)
Cervix	1 (0)	184 (6.0)	0 (0)	185 (6.0)
Vagina	0 (0)	66 (2.1)	0 (0)	66 (2.1)
Eye	18 (0.6)	7 (0.2)	0 (0)	25 (0.8)
Other	39 (1.3)	14 (0.5)	0 (0%)	53 (1.7)
Not Specified	3 (0.1)	1 (0)	0 (0)	4 (0.1)
Total	2,674 (86.5)	407 (13.2)	11 (0.4)	3,092 (100)

Figure 1. *Neisseria gonorrhoeae* Cases in Canada, 2000 to 2016[a]



[a]2016 total cases estimated based on 2015 numbers.

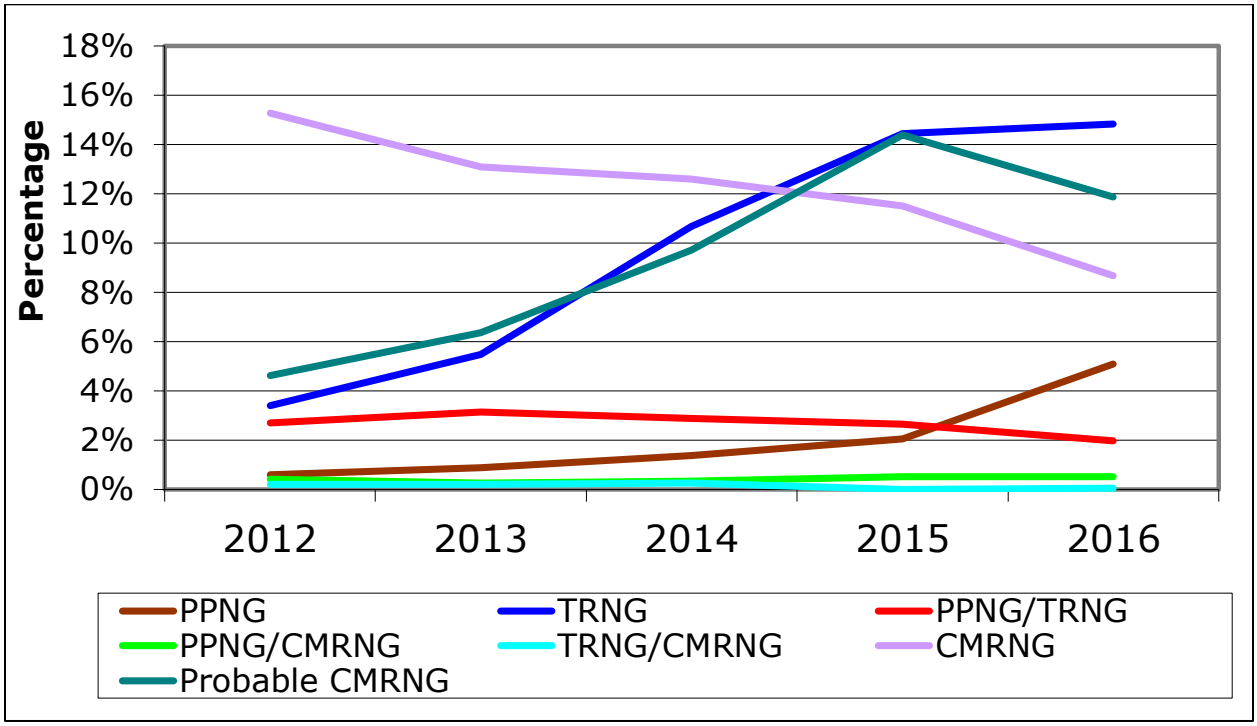
TRENDS IN ANTIMICROBIAL SENSITIVITIES

In 2016, 8.7% (393/4,538) of isolates were classified as Chromosomal Mediated Resistant *Neisseria gonorrhoeae* (CMRNG) (Figure 2). This proportion has been slowly decreasing since 2010 (21.8%, 648/2,970). This is due in part to the decline in penicillin resistance from 25.1% (744/2,970) in 2010 to 17.4% (791/4,538) in 2016 (Figure 3).

While penicillin resistance as a whole is decreasing, Penicillinase Producing *Neisseria gonorrhoeae* (PPNG) have been increasing. In 2012, they accounted for only 0.6% (18/3,036) of isolates tested. This proportion increased to 2.0% (85/4,190) in 2015 and to 5.1% (231/4,538) in 2016. PPNG/CMRNG has also shown a slight increase (Figure 2).

Tetracycline Resistant *Neisseria gonorrhoeae* (TRNG) increased significantly ($p<0.001$) from 5.5% (175/3,195) in 2013 to 14.4% (605/4,190) in 2015 but has remained stable at 14.8% (673/4,538) in 2016 (Figure 2).

Figure 2. Trends of PPNG, TRNG, CMRNG, Probable CMRNG *Neisseria gonorrhoeae* in Canada from 2012 to 2016[a]

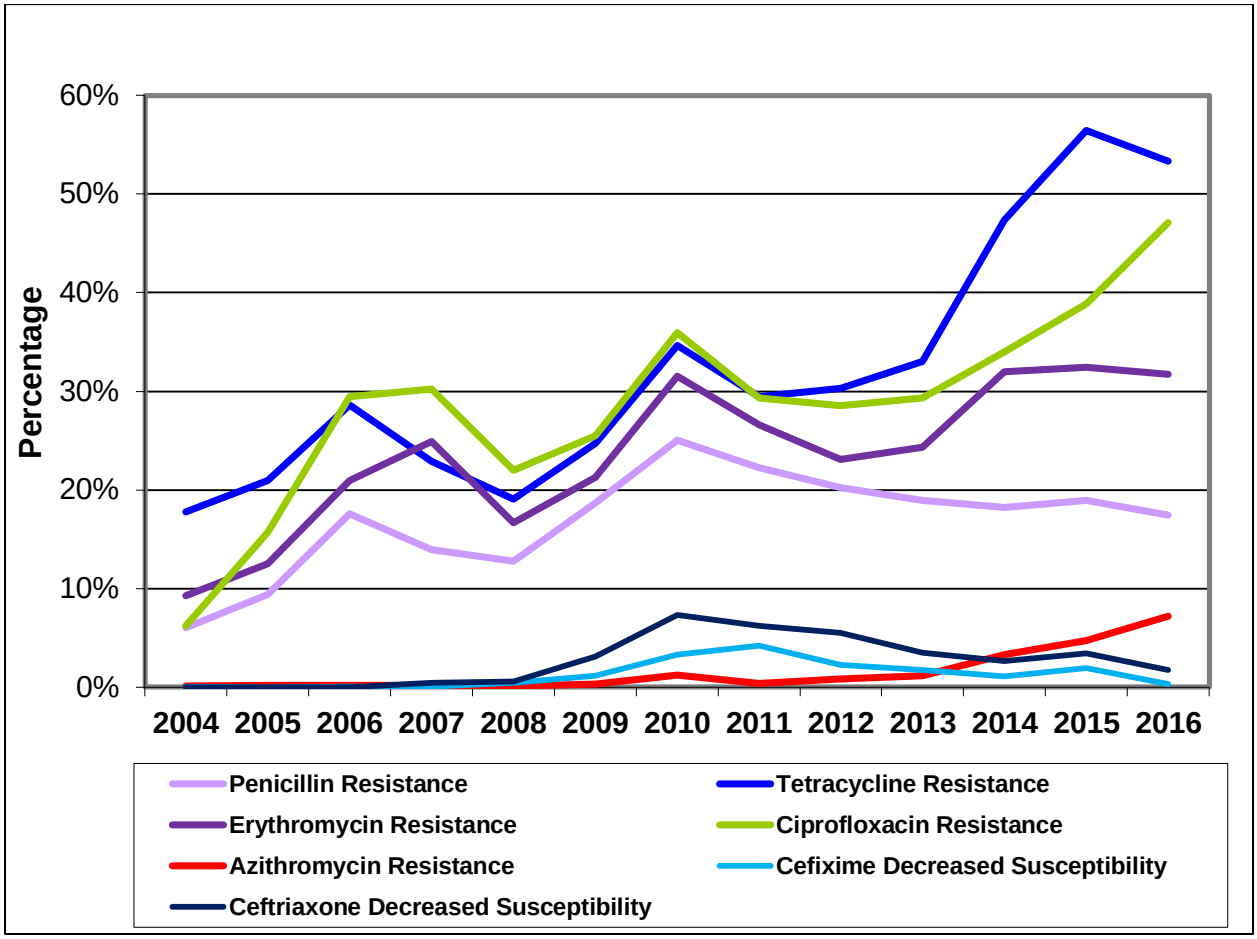


[a]Percentage based on total number of isolates tested nationally: 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538

Figure 3 represents the trends of antimicrobial susceptibilities of *N. gonorrhoeae* tested in Canada from 2004 to 2016.

Penicillin resistance increased from 6.0% (242/4,018) in 2004, to 25.1% (744/2,970) in 2010 and has since decreased to 17.4% (791/4,538) in 2016. Tetracycline resistance increased from 17.8% (715/4,018) in 2004 to 34.6% (1,028/2,970) in 2010. Between 2013 and 2015, tetracycline resistance increased from 33.0% (1054/3,195) to 56.4% (2,364/4,190) due to increases in both TRNG and chromosomal tetracycline resistance. In 2016, tetracycline resistance decreased slightly to 53.3% (2,319/4,538). In 2004, only 9.3% (373/4,018) of Canadian isolates were found to be erythromycin resistant. This percentage has increased gradually and is 31.7% (1,439/4,538) in 2016. The percentage of ciprofloxacin resistant isolates increased from 6.3% (251/4,018) in 2004 to 38.9% (1,629/4,190) in 2015. In 2016, it increased sharply to 47.1% (2,136/4,538). 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 in 2015 increased to 4.7% (198/4,190). In 2016, it increased significantly ($p<0.001$) to 7.2% (326/4,538). Decreased susceptibility to cefixime and ceftriaxone declined between 2015 [1.9% (80/4,190) and 3.5% (145/4,190), respectively] and 2016 [0.3% (14/4,538) and 1.8% (80/4,538), respectively]. Of the 10,045 viable isolates tested at NML between 2012 and 2016, none showed resistance to spectinomycin.

Figure 3. Trends of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Tested in Canada, 2004-2016[a]



[a]Percentage based on total number of isolates tested nationally: 2004=4,018; 2005=3,619; 2006=4,201; 2007=4,275; 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

THIRD GENERATION CEPHALOSPORINS

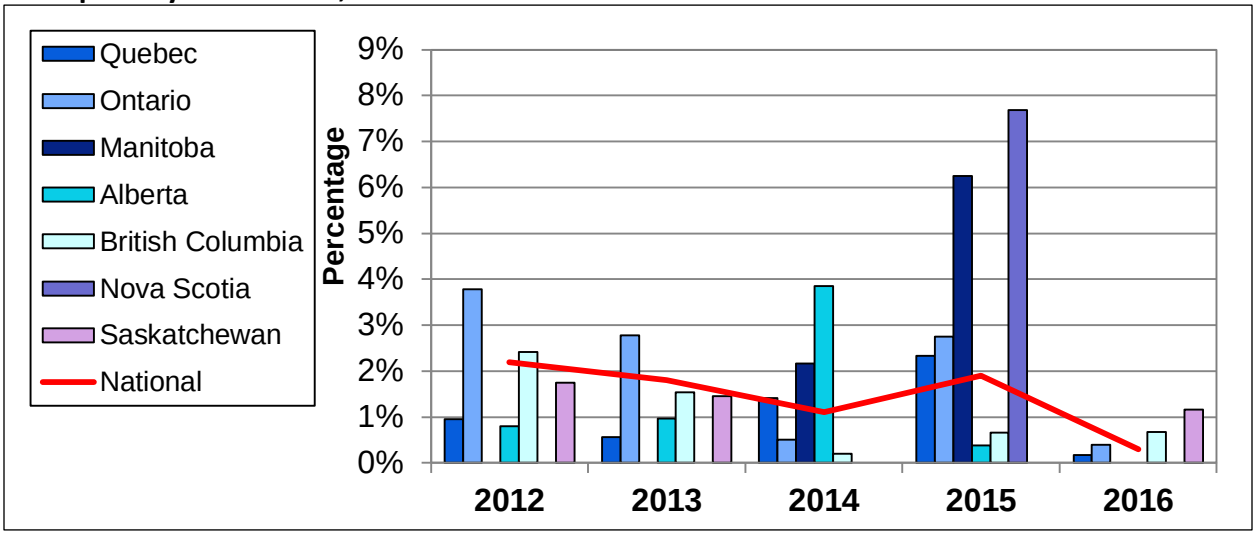
The downward trend of isolates with decreased susceptibilities to cephalosporins reversed in 2015 but declined again in 2016. According to WHO (2012) definitions (isolates with MIC≥0.25 mg/L for cefixime and ≥0.125 mg/L for ceftriaxone have decreased susceptibility), 0.3% of isolates (14/4,538) were identified as having decreased susceptibility to cefixime (Figure 4) and 1.8% (80/4,538) were identified as having decreased susceptibility to ceftriaxone (Figure 5).

In 2016, 2.0% (89/4,538) of isolates had decreased susceptibility to cefixime and/or ceftriaxone. This number represents a decrease from 4.4% (185/4,190) in 2015 and 3.1% (119/3,809) in 2014.

The geographical distribution of *N. gonorrhoeae* isolates with decreased susceptibility to cefixime and ceftriaxone within Canada are represented in Figures 4 and 5 and in Tables 6 and 7.

The modal MIC for cefixime has varied between 0.032 and 0.063 mg/L since 2012. The ceftriaxone modal MIC remained at 0.063 mg/L from 2010 through 2013 but decreased to 0.032 mg/L in 2014, 2015 and 2016 (Figures 6-9, Tables 8 and 9).

Figure 4. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Cefixime, 2012 to 2016[a]



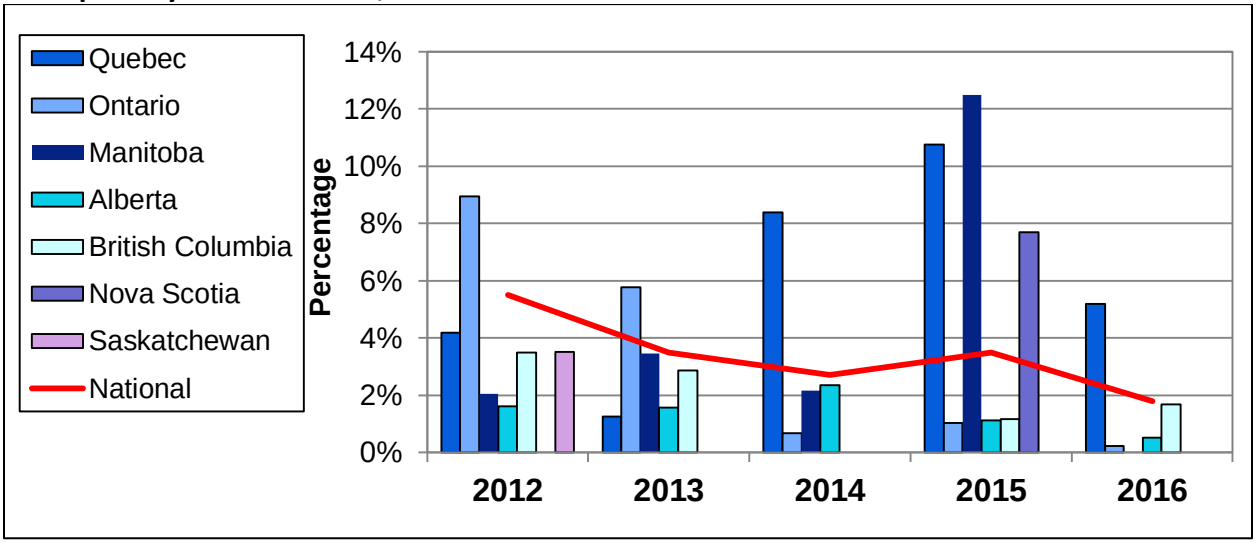
[a]Denominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 5. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Cefixime, 2012 to 2016[a]

Province	Year				
	2012	2013	2014	2015	2016
Quebec	8	4	13	23	2
Ontario	46	39	9	46	7
Manitoba	0	0	1	3	0
Alberta	4	5	18	3	0
British Columbia	9	7	1	4	4
Nova Scotia	0	0	0	1	0
Saskatchewan	1	1	0	0	1
Total No. of isolates	**68**	**56**	**42**	**80**	**14**
% CeDS of all isolates tested nationally	**2.2%**	**1.8%**	**1.1%**	**1.9%**	**0.3%**

[a]Percentage based on total number of isolates tested nationally: 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538

Figure 5. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Ceftriaxone, 2012 to 2016[a]



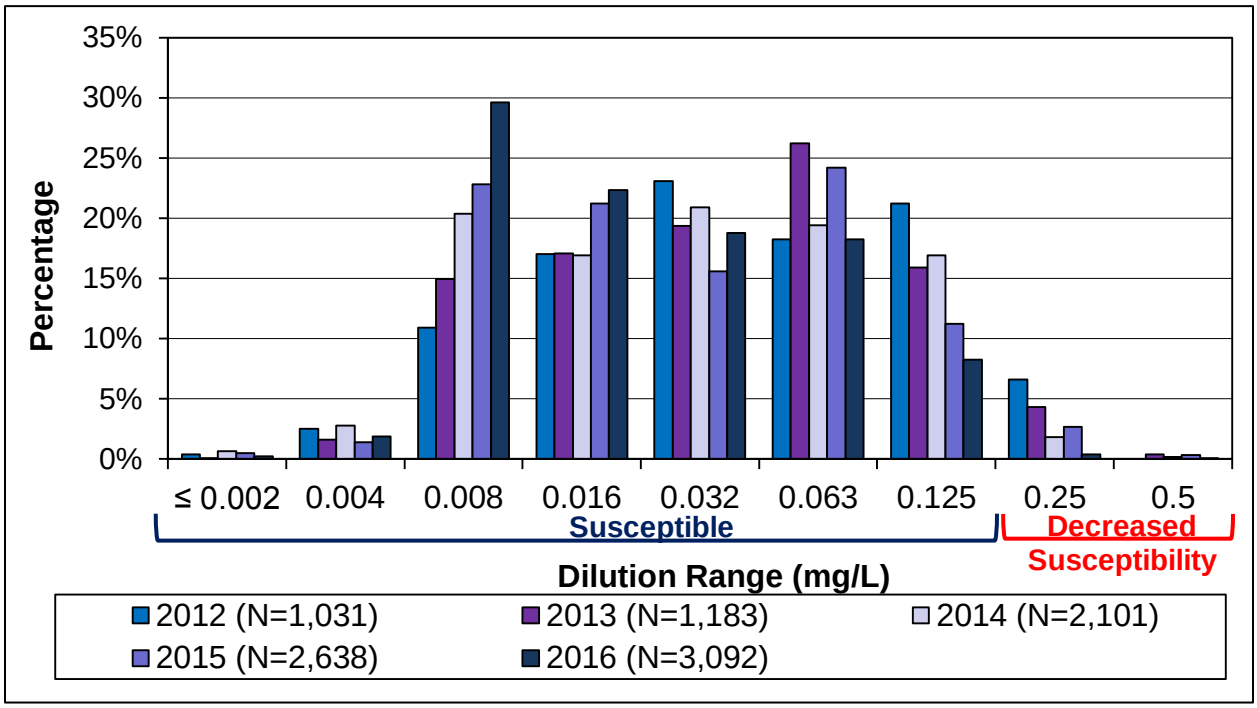
[a]Denominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 6. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Ceftriaxone, 2012 to 2016[a]

Province	Year				
	2012	2013	2014	2015	2016
Quebec	35	9	77	106	62
Ontario	109	81	12	17	4
Manitoba	1	1	1	6	0
Alberta	8	8	11	9	4
British Columbia	13	13	0	7	10
Nova Scotia	0	0	0	1	0
Saskatchewan	2	0	0	0	0
Total No. of isolates	**168**	**112**	**101**	**146**	**80**
% CxDS of all isolates tested nationally	**5.5%**	**3.5%**	**2.7%**	**3.5%**	**1.8%**

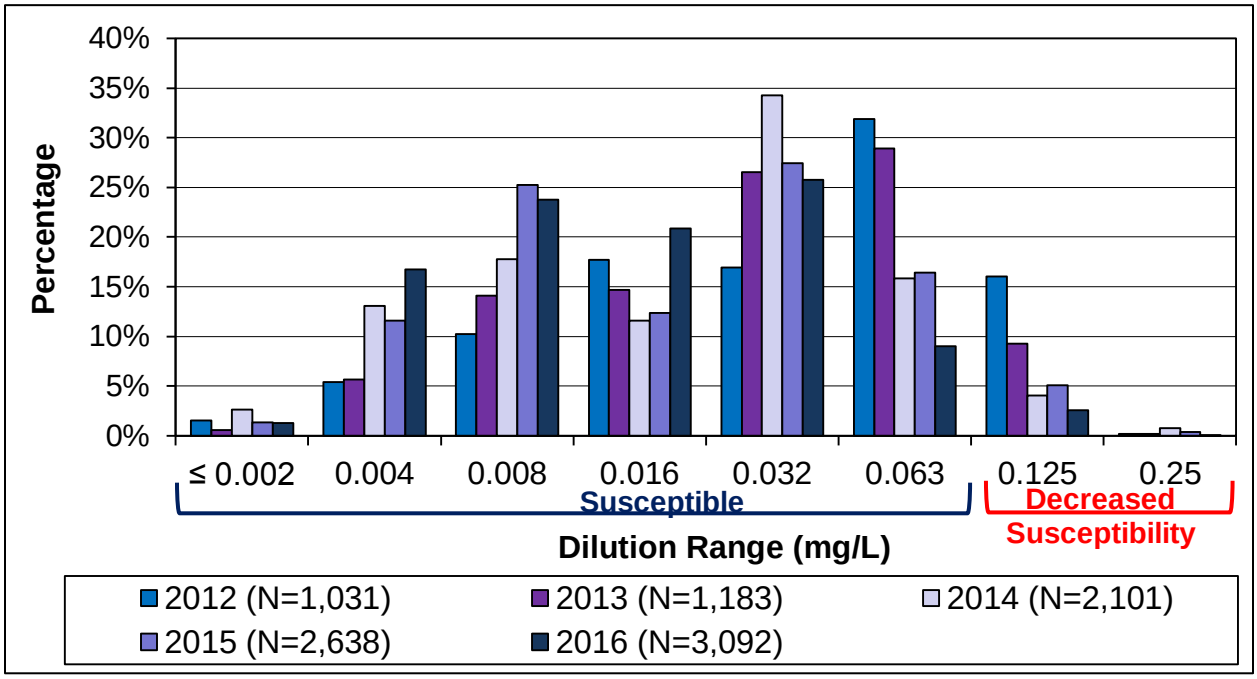
[a]Percentage based on total number of isolates tested nationally: 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538

Figure 6. Trends of Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[a]



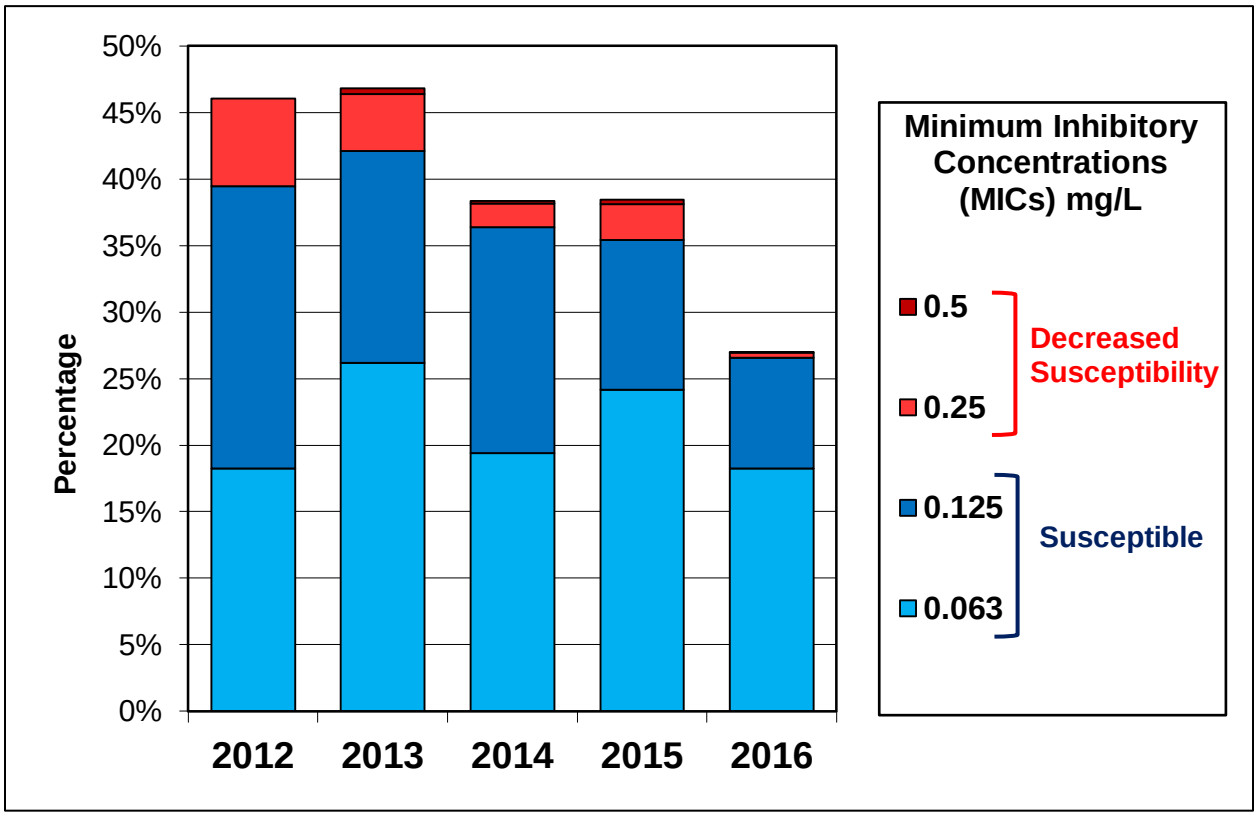
[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by NML as the denominator (N).

Figure 7. Trends of Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[a]



[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by NML as the denominator (N).

Figure 8. Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[ab]



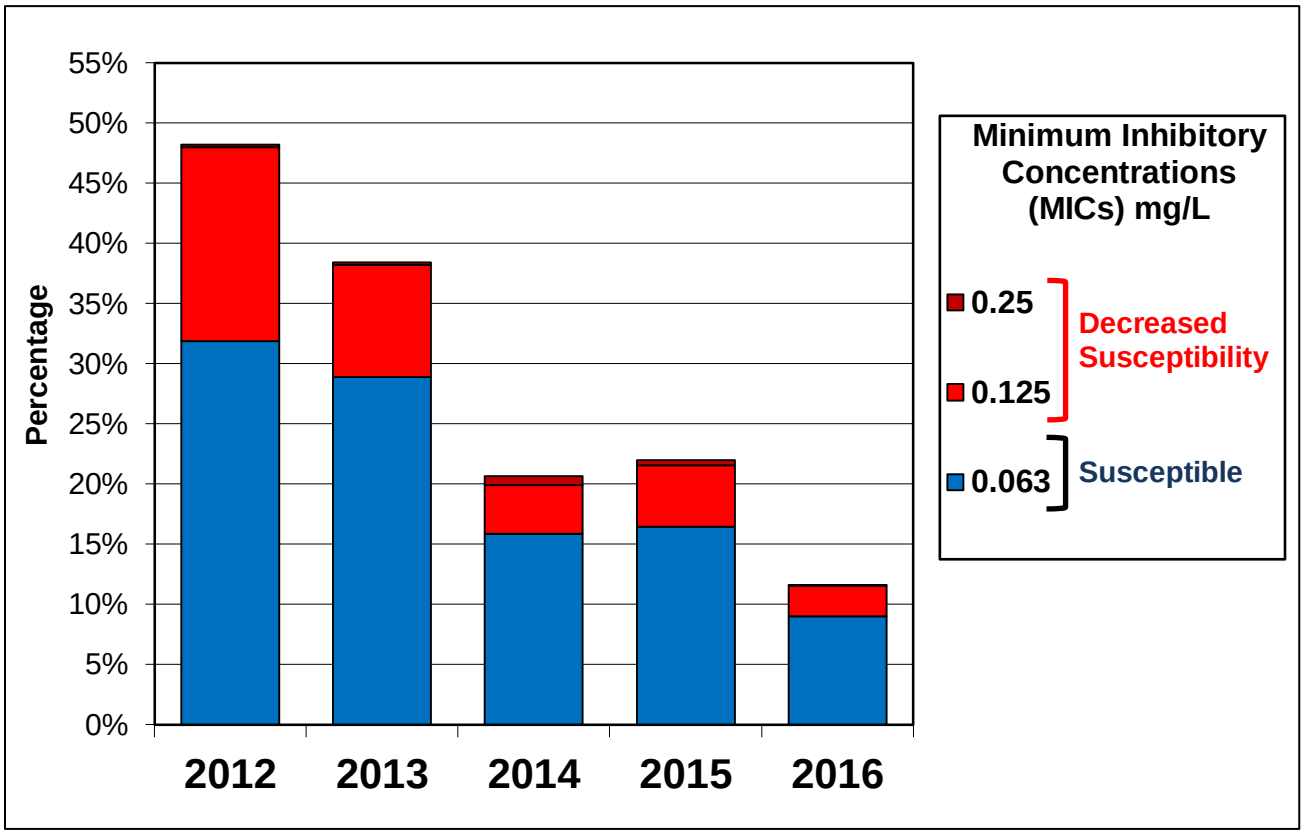
[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator 2012=1,031; 2013=1,183; 2014=2,101; 2015=2,638; 2016=3,092
[b]Isolates not represented on this chart had cefixime MICs <0.063 mg/L and were susceptible.

Table 7. Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[ab]

Dilutions (mg/L)	Interpretive Category	Year				
		2012	2013	2014	2015	2016
≤0.032 mg/L	Susceptible	54.1%	53.1%	60.7%	61.6%	73.0%
0.063 mg/L		18.2%	26.2%	19.4%	24.2%	18.3%
0.125 mg/L		21.2%	15.9%	16.9%	11.3%	8.3%
0.25 mg/L	Decreased Susceptibility	6.6%	4.3%	1.8%	2.7%	0.4%
0.5 mg/L		0.0%	0.4%	0.2%	0.3%	0.03%

[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2012=1,031; 2013=1,183; 2014=2,101; 2015=2,638; 2016=3,092
[b]Isolates not represented in this table had cefixime MICs <0.063 mg/L and were susceptible.

Figure 9. Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[ab]



[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2012=1,031; 2013=1,183; 2014=2,101; 2015=2,638; 2016=3,092
[b]Isolates not represented on this chart had ceftriaxone MICs <0.063 mg/L and were susceptible.

Table 8. Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates tested by the NML from 2012 to 2016[ab]

Dilutions (mg/L)	Interpretive Category	Year				
		2012	2013	2014	2015	2016
≤0.032 mg/L	Susceptible	51.8%	61.6%	78.2%	78.1%	88.4%
0.063 mg/L		31.9%	28.9%	15.9%	16.4%	9.0%
0.125 mg/L	Decreased Susceptibility	16.1%	9.3%	4.1%	5.1%	2.6%
0.25 mg/L		0.2%	0.2%	0.8%	0.4%	0.03%

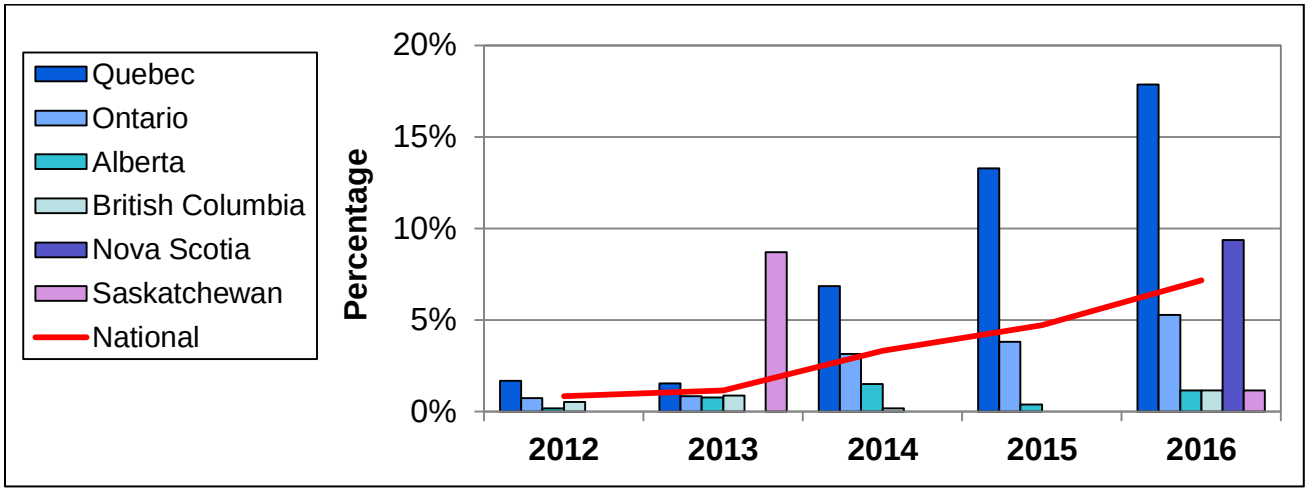
[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator 2012=1,031; 2013=1,183; 2014=2,101; 2015=2,638; 2016=3,092
[b]Isolates not represented in this table had ceftriaxone MICs <0.063 mg/L and were susceptible.

AZITHROMYCIN

The distribution of azithromycin resistant isolates across Canada is represented in Figure 10 and Table 9. Azithromycin resistant *N. gonorrhoeae* increased appreciably from 1.2% (37/3,195) in 2013 to 3.3% (127/3,809), 4.7% (198/4,190) and 7.2% (326/4,538) in 2014, 2015 and 2016, respectively.

The modal MIC for azithromycin remained at 0.5 mg/L between 2010 and 2012. From 2013 to 2016, the modal MIC was 0.25 mg/L (Figures 11 and 12 and Table 10), although there were a greater number of resistant isolates. Between 2009 and 2012, five isolates with high level azithromycin resistance (MIC≥256 mg/L) were identified in Canada.

Figure 10. Geographical Distribution of Azithromycin Resistant *Neisseria gonorrhoeae* Isolates, 2012 to 2016[a]



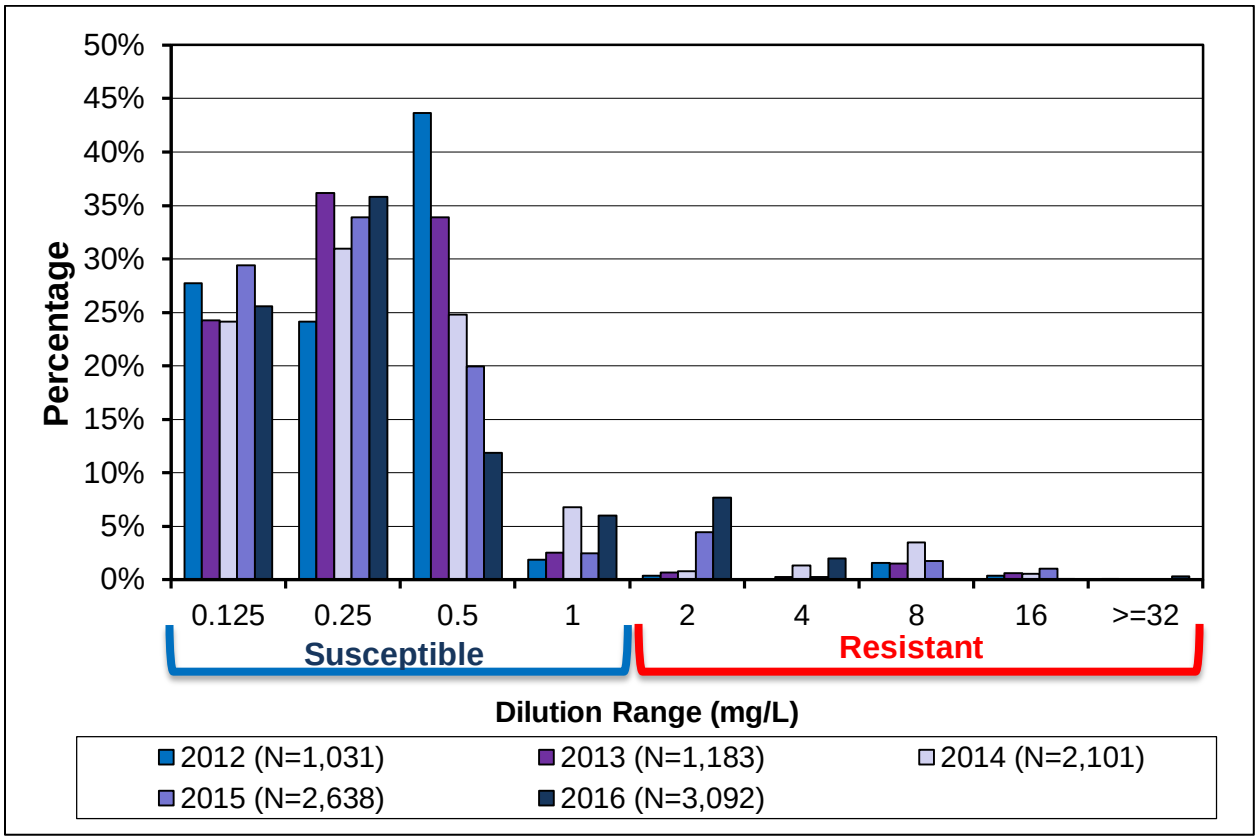
[a]Denominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 9. Geographical Distribution of Azithromycin Resistant *Neisseria gonorrhoeae* Isolates, 2012 to 2016[a]

Province	Year				
	2012	2013	2014	2015	2016
Quebec	14	11	63	131	214
Ontario	9	12	56	64	92
Alberta	1	4	7	3	9
British Columbia	2	4	1	0	7
Nova Scotia	0	0	0	0	3
Saskatchewan	0	6	6	0	1
Total No. of AzR isolates	26	37	127	198	326
% AzR of all isolates tested nationally	**0.9%**	**1.2%**	**3.3%**	**4.7%**	**7.2%**

[a]Percentage based on total number of isolates tested nationally: 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538

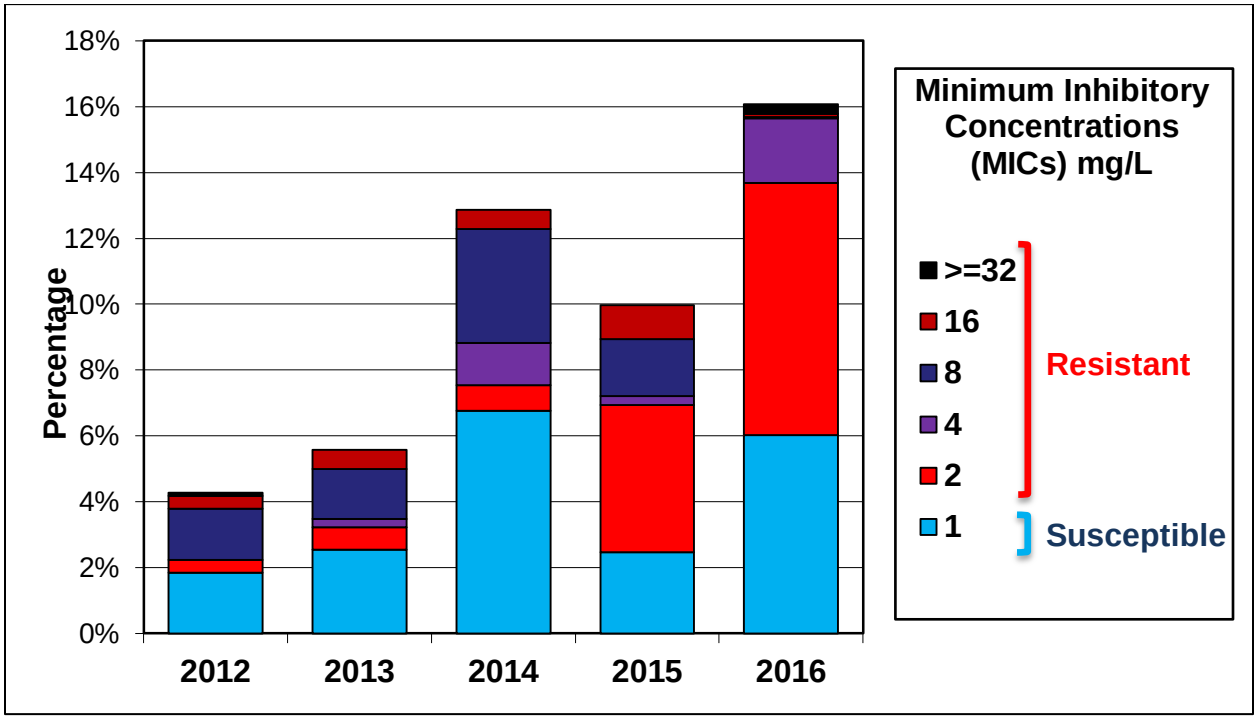
Figure 11. Trends of Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[ab]



[a]Percentages were calculated using the total number of viable strains (both resistant and susceptible isolates) tested by NML as the denominator (N).

[b]Isolates not represented on this chart had azithromycin MICs <0.125 mg/L and were susceptible.

Figure 12. Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2012 to 2016[ab]



[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2012=1,031; 2013=1,183; 2014=2,101; 2015=2,638; 2016=3,092
[b]Isolates 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 2012 to 2016[ab]

Dilution (mg/L)	Interpretive Category	Year				
		2012	2013	2014	2015	2016
≤0.5 mg/L	Susceptible	95.7%	94.4%	85.8%	90.0%	83.4%
1 mg/L		1.8%	2.5%	6.8%	2.5%	6.0%
2 mg/L	Resistant	0.4%	0.7%	0.8%	4.5%	7.7%
4 mg/L		0%	0.3%	1.3%	0.3%	2.0%
8 mg/L		1.6%	1.5%	3.5%	1.7%	0.03%
16 mg/L		0.4%	0.6%	0.6%	1.0%	0.1%
≥32 mg/L		0.1%	0%	0%	0%	0.3%

[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2012=1,031; 2013=1,183; 2014=2,101; 2015=2,638; 2016=3,092
[b]Isolates not represented on this table had azithromycin MICs <0.25mg/L and were susceptible.

CO-RESISTANCE – AZITHROMYCIN AND CEPHALOSPORINS

In 2012, seven isolates with a combined decreased susceptibility to cephalosporins and resistance to azithromycin 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. In 2016, 1 isolate (0.02%, 1/4,538) with both decreased susceptibility to cephalosporins and resistance to azithromycin was identified (Table 11).

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

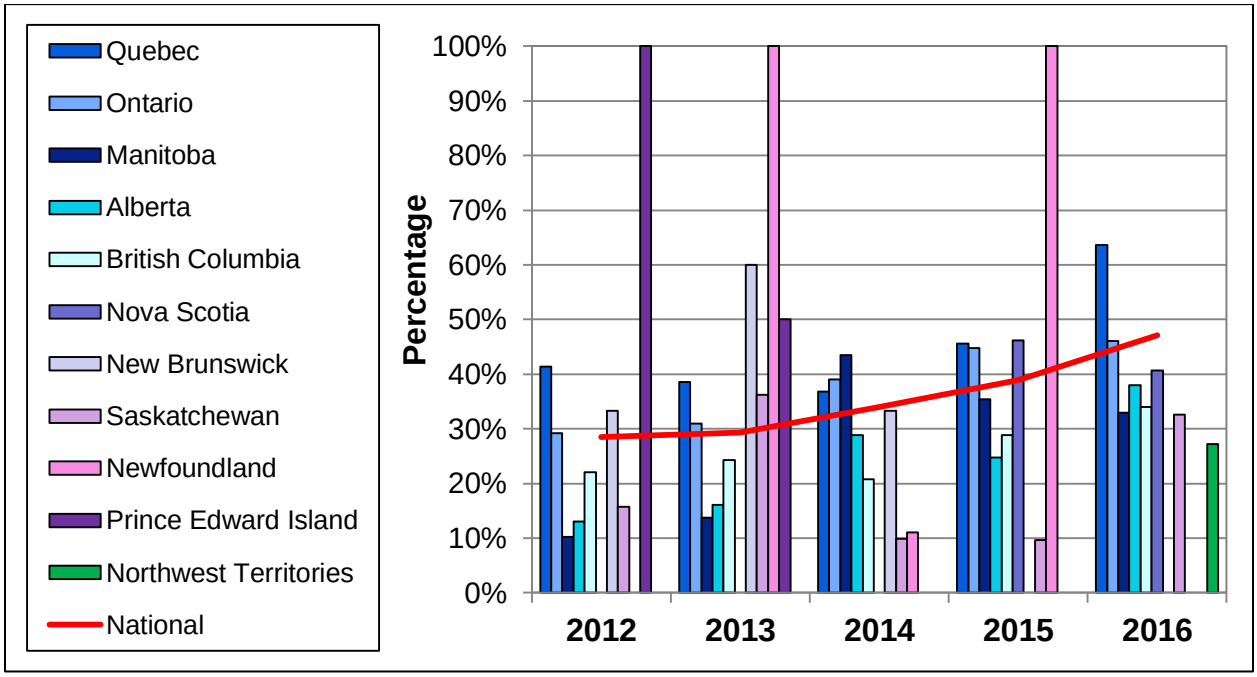
Year	Number of AziR Isolates	Percent AziR[a]	Number of AziR Isolates with CeDS and/or CxDS	Percent AziR Isolates with CeDS and/or CxDS[a]	NG-MAST of AziR with CeDS and/or CxDS	Provinces
2012	26	0.9%	7	0.2%	ST-3158 (6); ST-1407 (1)	BC (1), ON (6)
2013	37	1.2%	8	0.3%	ST-3158 (6); ST-1407 (1); ST-9427 (1)	BC (2), SK (1), ON (5)
2014	127	3.3%	1	0.03%	ST-1407	QC
2015	198	4.7%	2	0.05%	ST-11765, ST-2400	ON, QC
2016	326	7.2%	1	0.02%	ST-2318	BC

[a]Percentage based on the number of isolates tested nationally: 2011=3,360; 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538

CIPROFLOXACIN

The percentage of ciprofloxacin resistant isolates increased from 38.9% (1,629/4,190) in 2015 to 47.1% (2,136/4,538) in 2016. Percentages for each province are represented in Figure 13 and Table 12. Of the 2,136 ciprofloxacin resistant isolates identified in 2016, 87.9% (1,877/2,136) were also resistant to at least one other antibiotic; 17.1% (365/2,136) were characterized as CMRNG.

Figure 13. Geographical Distribution of Ciprofloxacin Resistant *Neisseria gonorrhoeae* Isolates, 2012 to 2016[a]



[a]Denominators 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, 2012 to 2016[a]

Province	Year				
	2012	2013	2014	2015	2016
Quebec	347	276	338	479	761
Ontario	356	434	690	750	800
Manitoba	5	4	20	17	28
Alberta	65	83	135	196	299
British Columbia	82	110	102	174	204
Nova Scotia	0	0	0	6	13
New Brunswick	1	3	1	0	0
Saskatchewan	9	25	9	6	28
Newfoundland	0	1	1	1	0
Prince Edward Island	1	1	0	0	0
Northwest Territories	0	0	0	0	3
Total No. of CipR isolates	**866**	**937**	**1,296**	**1,629**	**2,136**
%CipR of all isolates tested nationally	**28.5%**	**29.3%**	**34.0%**	**38.9%**	**47.1%**

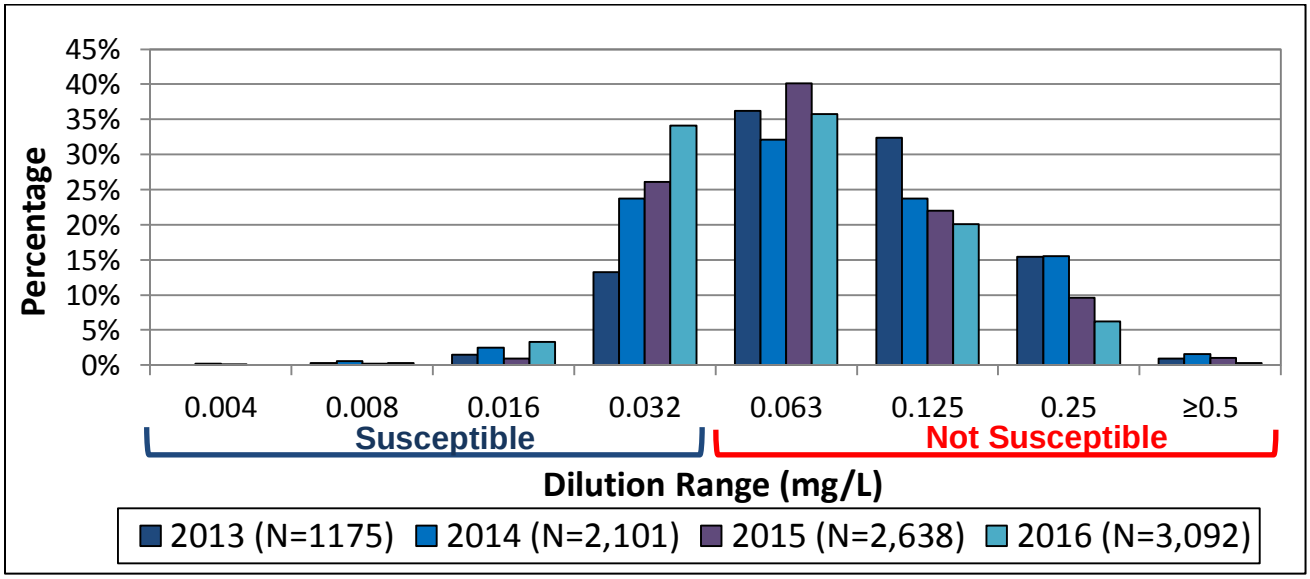
[a]Percentage based on total number of isolates tested nationally: 2012=3,036; 2013=3,195; 2014=3,809; 2015=4,190; 2016=4,538

ERTAPENEM

The NML began testing ertapenem late in 2012. From 2013 to 2016, the ertapenem modal MIC was 0.063 mg/L (Figure 14).

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 of 0.064 mg/L and 0.125 mg/L are not susceptible (NS).

Figure 14. Trends of Ertapenem Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2013 to 2016[a]



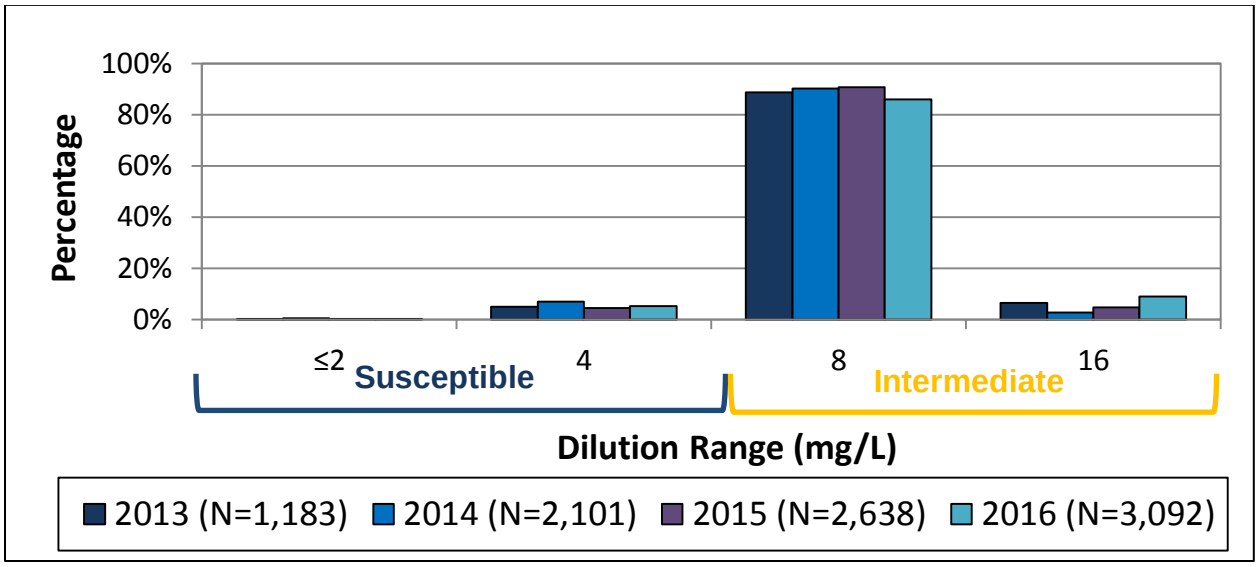
[a]Percentages were calculated using the total number of viable strains (both resistant and susceptible isolates) tested by NML as the denominator (N).

GENTAMICIN

The NML began testing gentamicin late in 2012. The gentamicin modal MIC for all isolates tested from 2013 to 2015 is 8 mg/L (Figure 15).

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

Figure 15. Trends of Gentamicin Susceptibilities of *Neisseria gonorrhoeae* Isolates Tested by the NML from 2013 to 2016[a]



[a]Percentages 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 2016, the most common sequence types (STs) identified by the NML were ST-5985 [11.9% (368/3,092)], ST-12302 [10.5% (324/3,092)] and ST-10451 [5.7% (177/3,092)] (Figure 16).

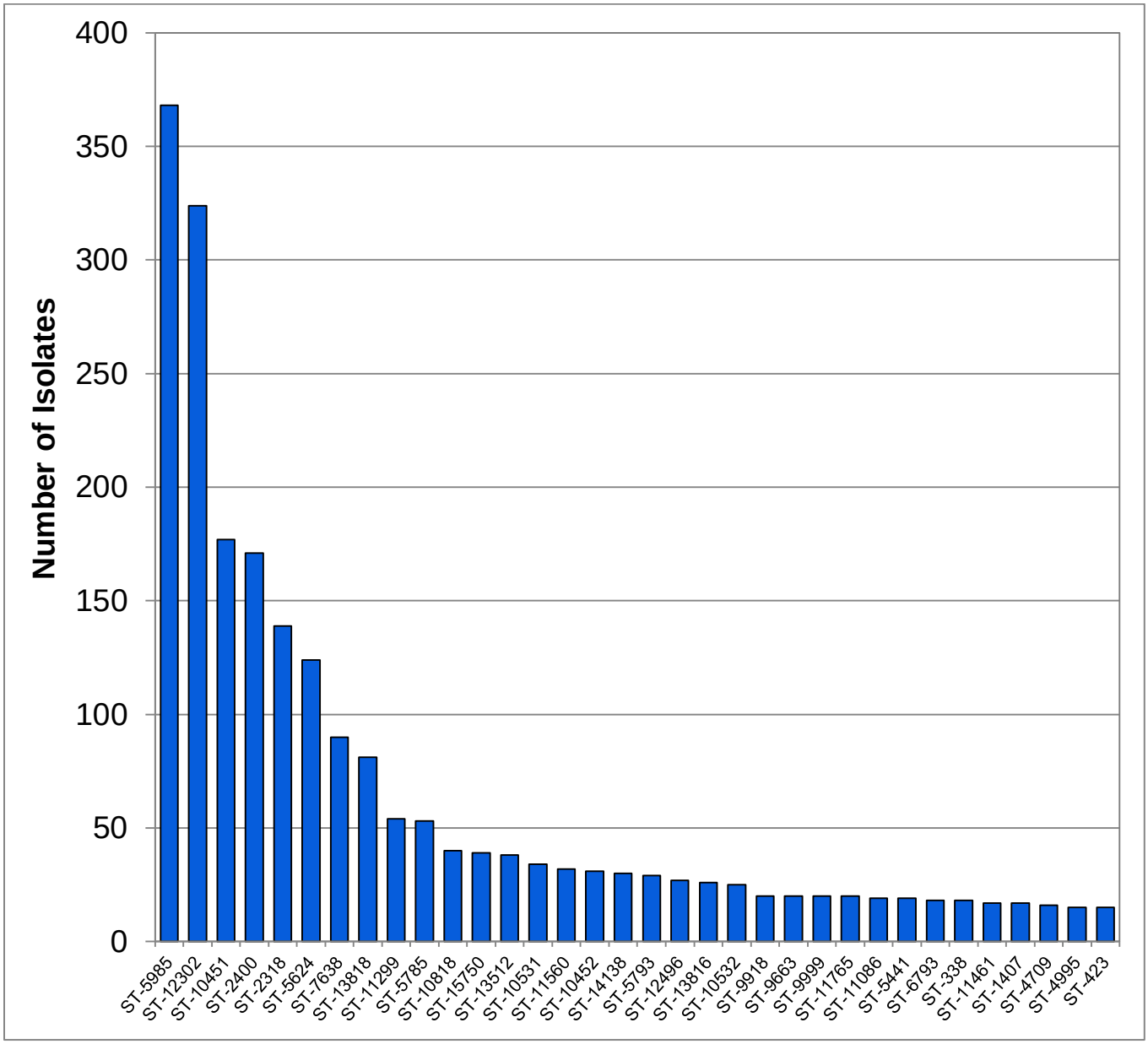
ST-5985 increased in prevalence from 0.6% in 2012 to 15.1% in 2015 and has since decreased to 11.9% in 2016 (Figure 17). In 2016, 13.6% (420/3,092) of Canadian isolates belonged to the ST-5985 genogroup and included these highly related sequence types: ST-14031 (n=11), ST-13572 (n=9), ST-11868 (n=9), ST-14518 (n=6), ST-14686 (n=6), ST-15746 (n=2) and ST-6968 (n=2), plus 7 other single ST types. Isolates of this genogroup are primarily TRNGs [86.2% (362/420)].

The proportion of ST-12302 isolates increased from 4.3% in 2015 to 10.5% in 2016 (Figure 17). Canadian isolates identified in 2016 that are highly related to ST-12302 (Figure 22) include ST-15750 (n=39), ST-14502 (n=6), ST-3935 (n=4) plus 13 other STs with one to three isolates in each for a total of 393. Isolates of this genogroup are resistant to multiple drugs with 71.5% also resistant to azithromycin. There are no isolates with decreased susceptibility to cefixime or ceftriaxone in this genogroup (Figure 20).

ST-10451, the 3rd most prevalent ST in 2016 (5.7%), is a member of the ST-1407 genogroup as it differs from ST-1407 (n=17) by only 1 base pair, isolates with these 2 STs have similar antimicrobial resistance profiles (Figure 22). ST-1407 is an internationally identified clone that has been described as a superbug, harbouring high-level resistance to cephalosporins (Allen, 2013; Unemo, 2010; Unemo, 2011; Unemo, 2012). ST-1407 was the prevalent ST in 2010, 2011 and 2012. By 2016, only 0.6% (17/3,092) of isolates were identified as ST-1407 (Figure 17). Other isolates in the ST-1407 genogroup identified in 2016 are ST-11765 (n=20), ST-6793 (n=18), ST-14317 (n=8), ST-14927 (n=6) and ST-15757 (n=6) plus 13 other STs with one to three isolates in each. These highly related isolates are characterized with either the *tbp*B-110 allele and have *por* alleles that differ from *por*-908 by up to 2 nucleotide base pairs, or, are *por*-6106 (the *por* allele of ST-10451) and have *tbpB* alleles that differ from *tbpB*-110 by up to 2 nucleotide base pairs. A total of 8.8% of isolates (273/3,092) were either ST-10451 or highly related sub-types of ST-10451. The isolates in 2016's ST-1407 genogroup are primarily multidrug resistant, 5.5% (15/273) were resistant to azithromycin and 1 isolate had decreased susceptibility to cefixime and ceftriaxone (Figure 20).

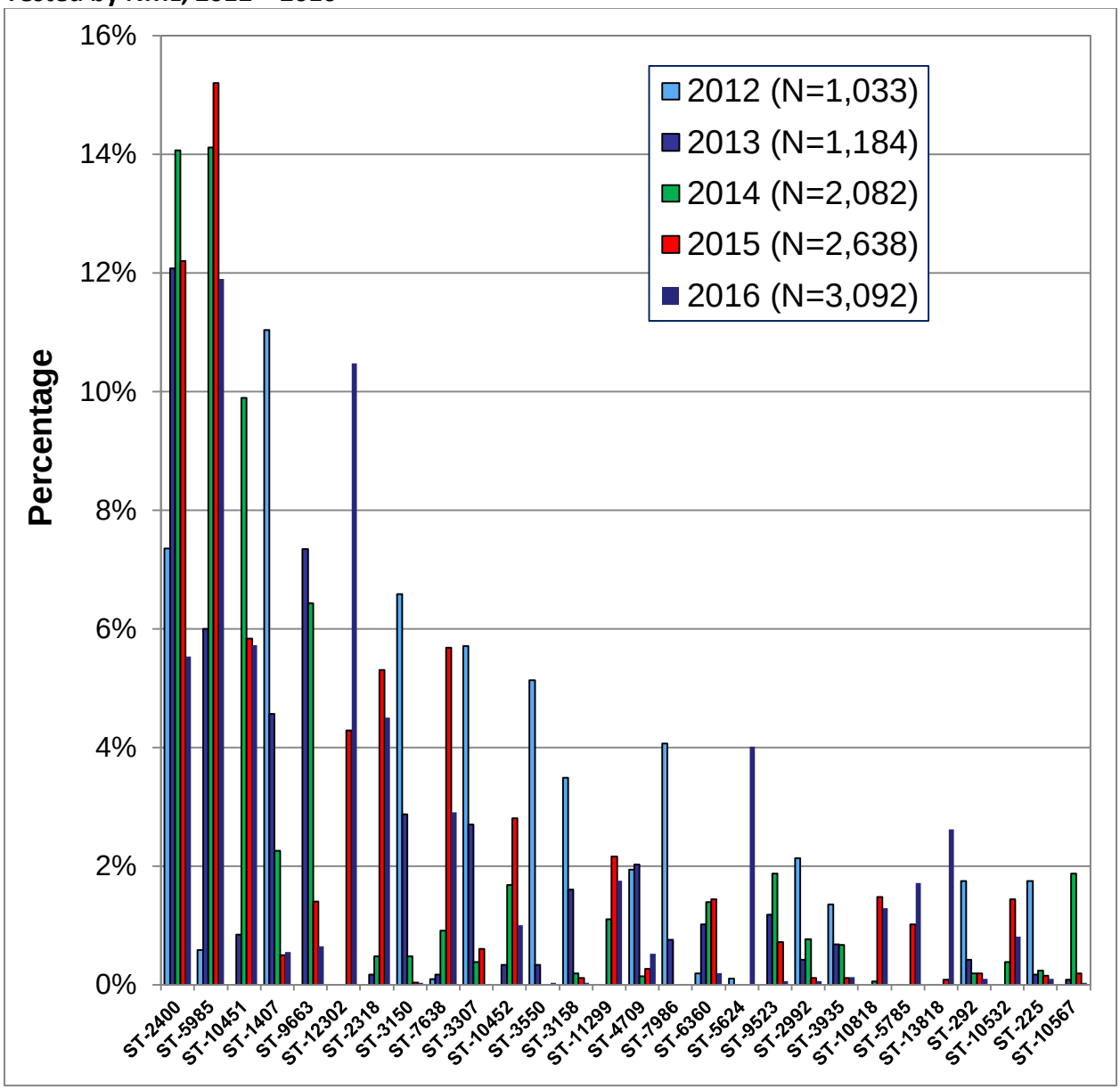
Distribution of STs within provinces is represented in Figures 18 and 19.

Figure 16. Prevalent NG-MAST Sequence Type Distribution of *Neisseria gonorrhoeae* Isolates Tested by the NML, 2016; N=3,092[a]



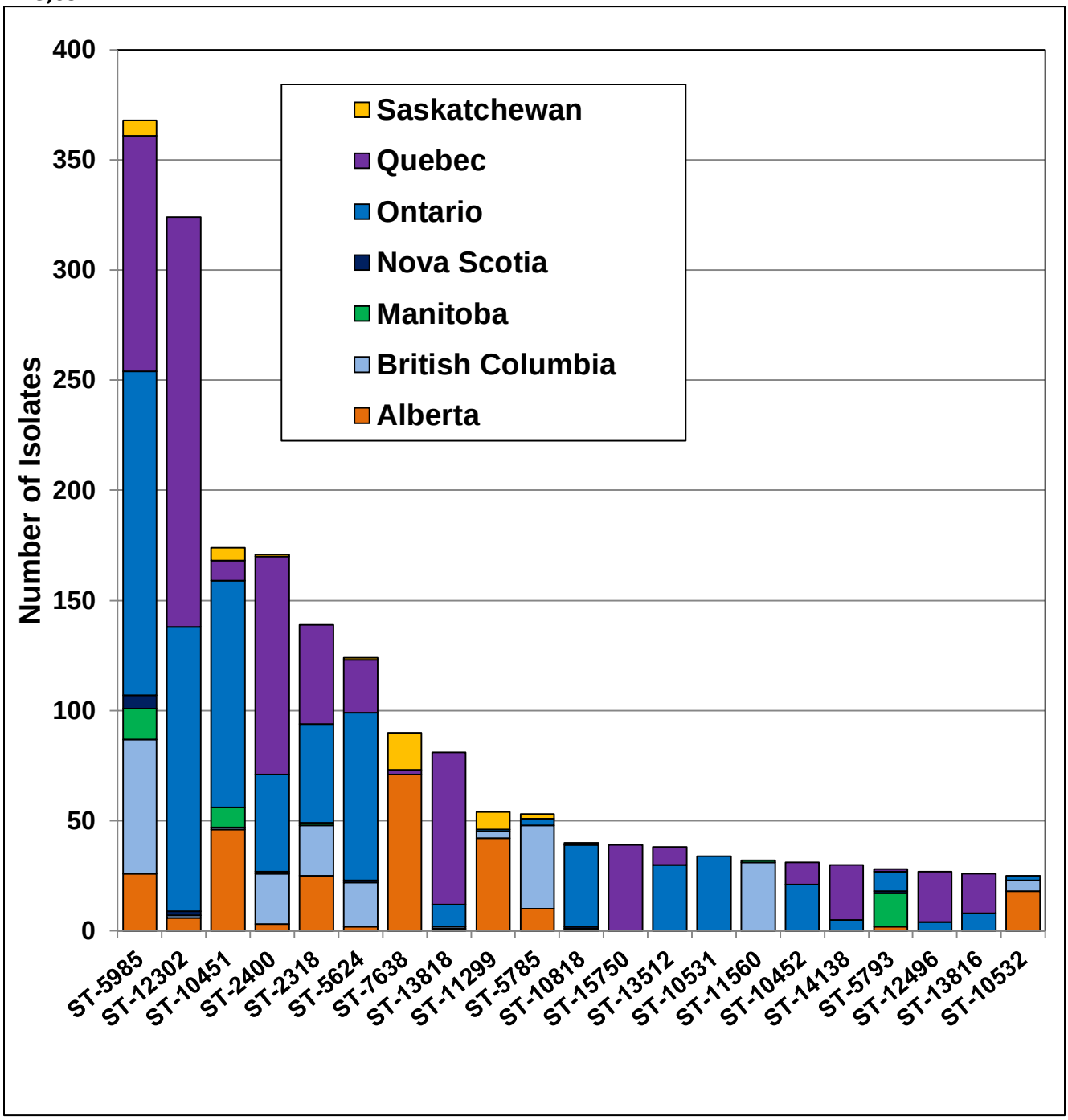
[a]This graph represents 2,166 isolates. The remaining 926 isolates are dispersed among 456 sequence types (STs) containing 1 to 13 isolates each.

Figure 17. Trends of Prevalent NG-MAST Sequence Types of *Neisseria gonorrhoeae* Isolates Tested by NML, 2012 – 2016[a]



[a]A total of 258 sequence types were identified in 2012, 292 sequence types in 2013, 378 sequence types in 2014, 396 sequence types in 2015 and 490 sequence types in 2016. Only the most prevalent sequence types of 2012 to 2016 are represented in this graph.

Figure 18. Provincial Distribution within *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2016; N=3,092[ab]



[a]This graph represents 1,932 isolates. The remaining 1,160 isolates are dispersed among 469 sequence types (STs) containing 1 to 20 isolates each.

[b]Not included in this graph is 1 ST-5793 isolate from New Brunswick

Figure 19. Distribution of *Neisseria gonorrhoeae* NG-MAST Sequence Types within Provinces, 2016; N=3,092[a]

[a]**New Brunswick (N=3):** ST-25 (n=1), ST-3935 (n=1), ST-5793 (n=1)

Nova Scotia (N=31): ST-5985 (n=6), ST-25 (n=4), ST-6819 (n=3), **ST-12302 (n=2),** ST-26 (n=2), ST-2400 (n=1) plus 13 additional STs with 1 isolate each.

Northwest Territories (N=4): ST-10451 (n=3), ST-4637 (n=1)

Figure 19a. Distribution of NG-MAST within Alberta (N=544)

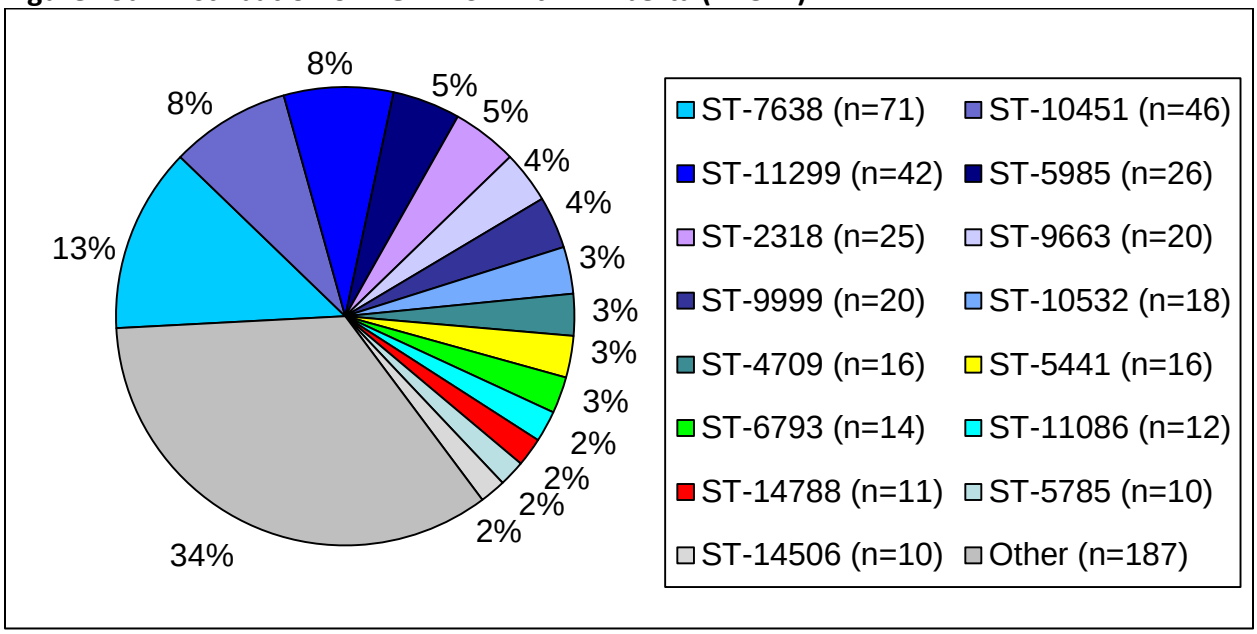


Figure 19b. Distribution of NG-MAST within British Columbia (N=348)

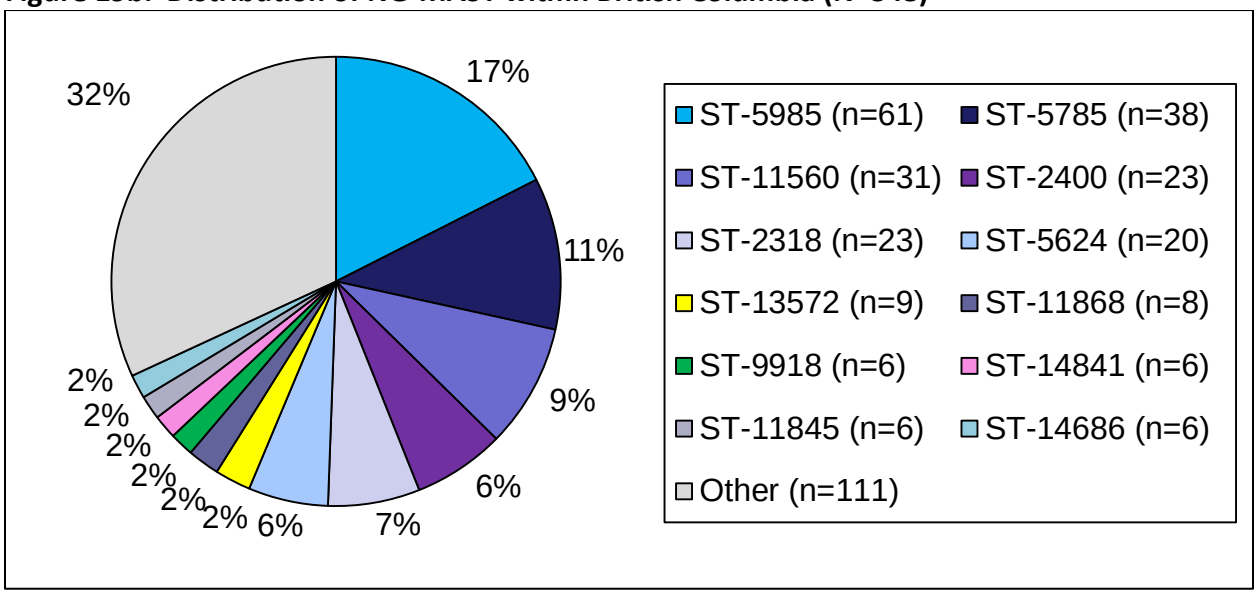


Figure 19c. Distribution of NG-MAST within Saskatchewan (N=85)

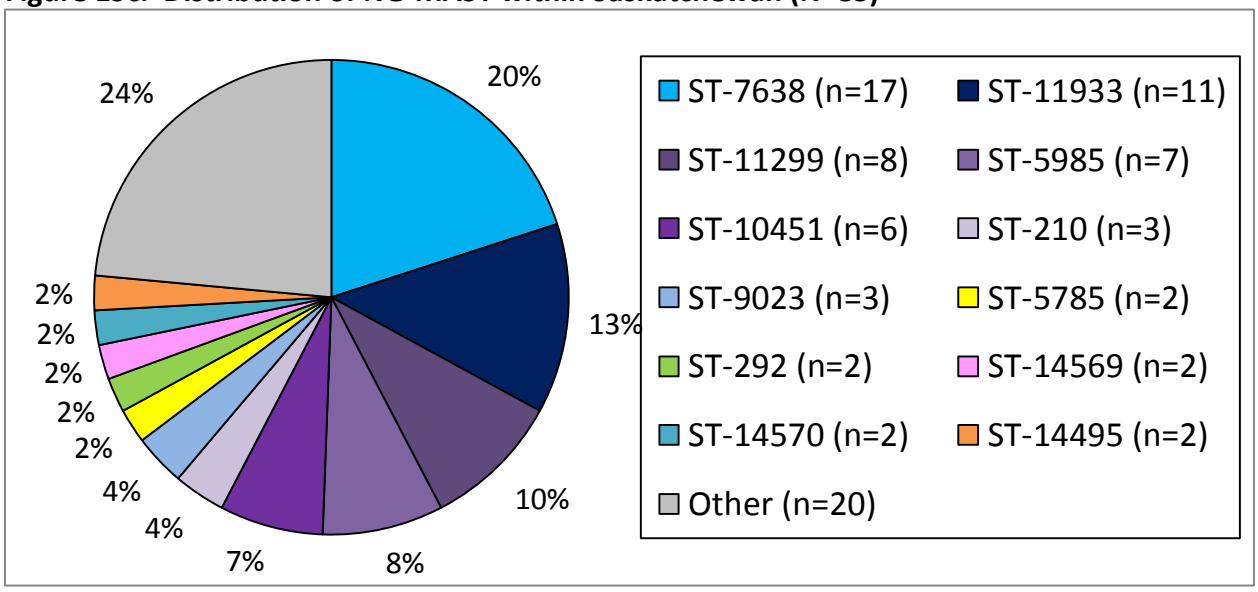


Figure 19d. Distribution of NG-MAST within Manitoba (N=82)

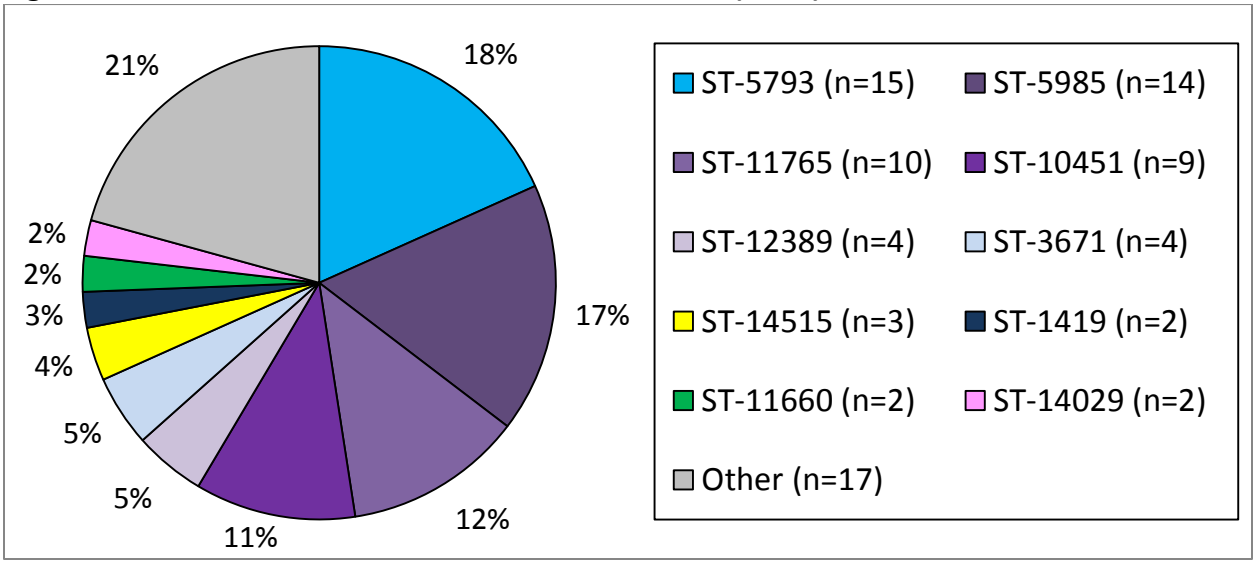


Figure 19e. Distribution of NG-MAST within Ontario (N=1,068)

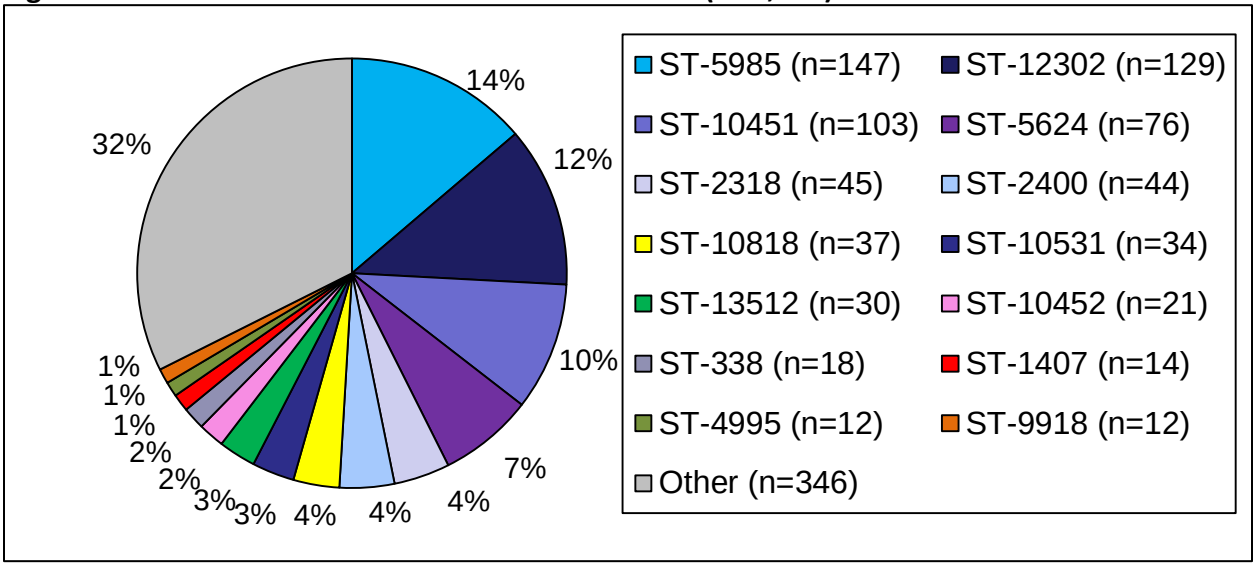


Figure 19f. Distribution of NG-MAST within Quebec (N=927)

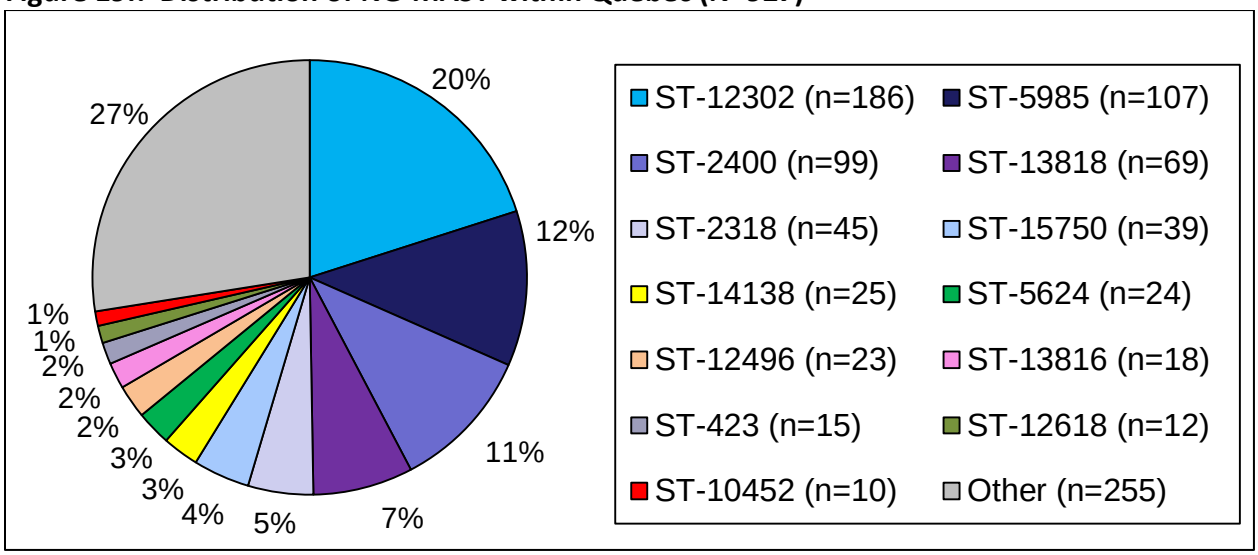
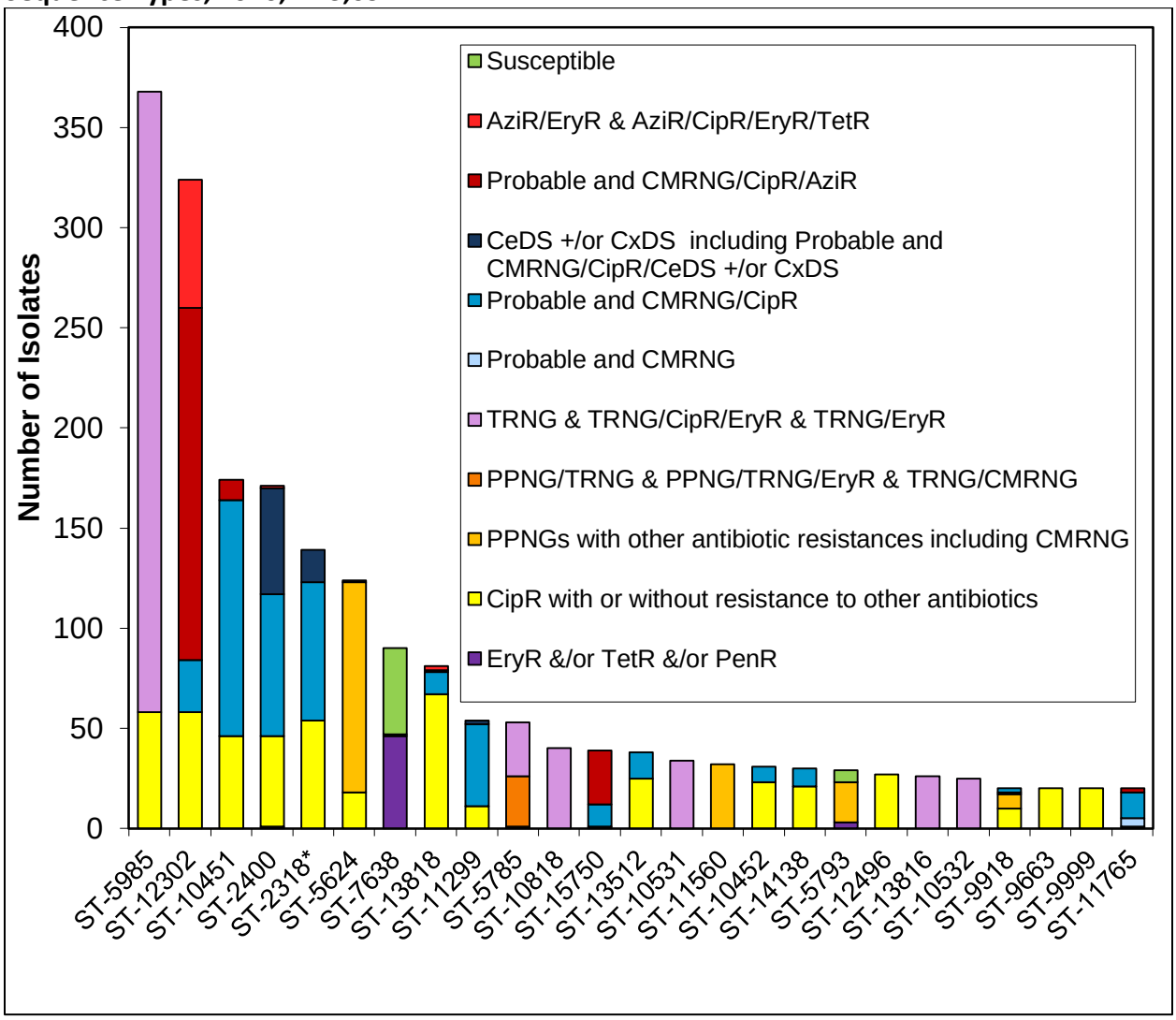


Figure 20. Distribution of Resistance Characterizations within *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2016; N=3,092[a]



[a]This graph represents 2,012 isolates. The remaining 1,080 isolates are dispersed among 465 sequence types (STs) containing 1 to 19 isolates each.
*__ST-2318__ has 1 isolate that is __CMRNG/AziR/CxDS/CipR__

Figure 21 outlines the NG-MAST sequence types of isolates with decreased susceptibility to cefixime (Figure 21a), decreased susceptibility to ceftriaxone (Figure 21b), azithromycin resistant isolates (Figure 21c) and susceptible isolates (Figure 21d).

The most prevalent ST of isolates with decreased susceptibility to cefixime in 2016 was ST-14410 [21.4% (3/14)] which is part of the ST-7554 genogroup (STs differ by ≤ 2 base pairs). ST-7554 was the predominant ST among isolates with decreased susceptibility to cefixime in 2015 [50% (40/80)] (Figure 21a).

Isolates with decreased susceptibility to ceftriaxone were primarily ST-2400 [66.3% (53/80)] followed by ST-2318 [20.0% (16/80)]. ST2318 along with 2 other STs (ST-12705 and ST-14911) are part of the same genogroup, differing by ≤ 2 base pairs. ST-14410 [2.5% (2/80)] and ST-13876 [1.3% (1/80)] are part of the ST-7554 genogroup which contained approximately 10% of the 2015 isolates with decreased susceptibility to ceftriaxone (Figure 21b).

The ST types identified among the AziR isolates are displayed in Figure 21c. ST-12302 [73.6% (240/326)], ST-15750 [8.3% (27/326)], ST-14698 [1.8% (6/326)], ST-14502 [0.9% (3/326)] and ST-5961 [0.6% (2/326)] differ by ≤ 2 base pairs and are responsible for 85.3% (278/326) of the 2016 azithromycin resistant isolates. ST-10451 [3.1% (10/326)], ST-11765 [0.6% (2/326)] and ST-14277 [0.6% (2/326)] are also closely related and responsible for 4.3% (14/326) of 2016 azithromycin resistant isolates.

The STs of the susceptible isolates available for testing included ST-7638 [27.4% (43/157)] and ST-14788 [5.1% (8/157)] which differ by only 1 base pair and are responsible for 32.5% (51/157) of the susceptible isolates submitted to the NML in 2016. ST-25, ST-4637 and ST-6819 differ by ≤ 4 base pairs and make up 9.6% (15/157) of the susceptible isolates tested at the NML (Figure 21d).

Figure 21. NG-MAST Sequence Types of 2016 *Neisseria gonorrhoeae* Isolates

Figure 21a. Decreased Susceptibility to Cefixime (MIC ≥ 0.25 mg/L), N=14

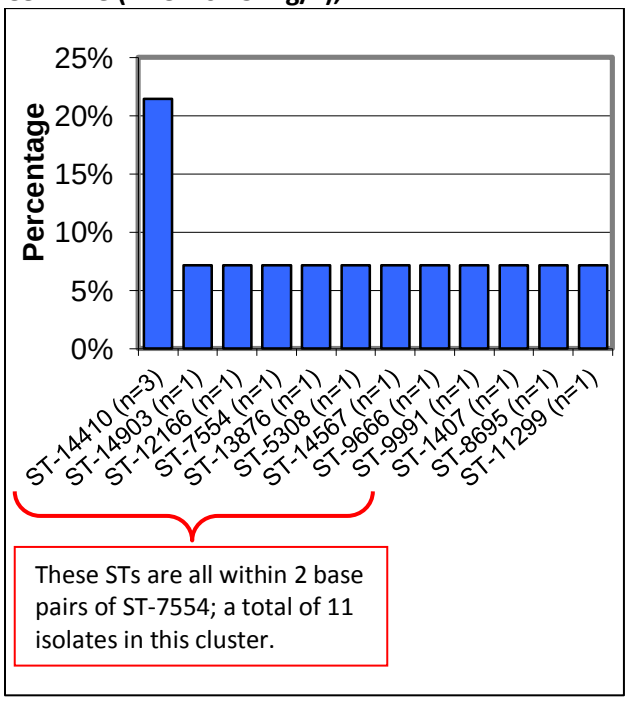


Figure 21b. Decreased Susceptibility to Ceftriaxone (MIC ≥ 0.125 mg/L), N=80

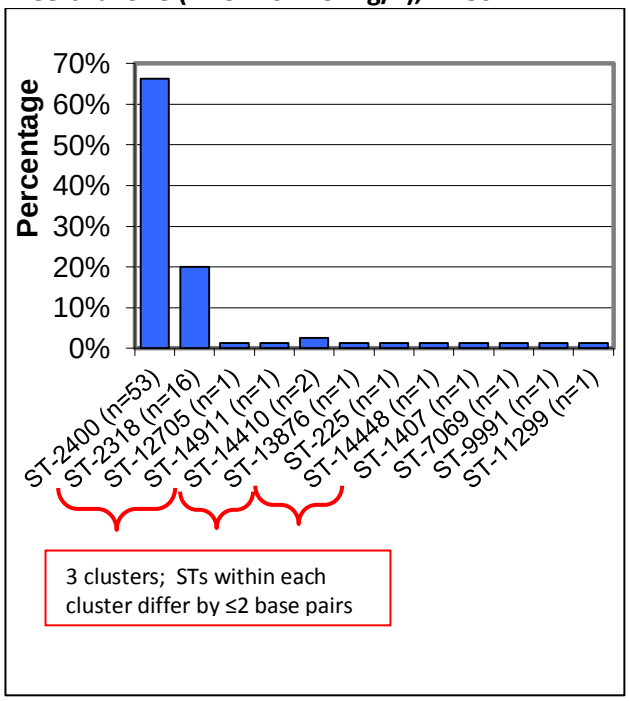


Figure 21c. Azithromycin Resistant (MIC ≥ 2 mg/L), N=326[a]

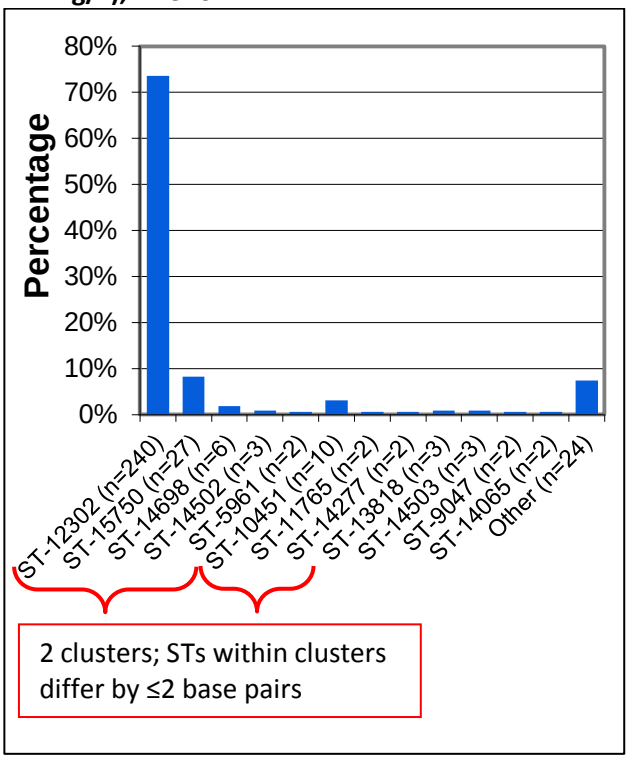
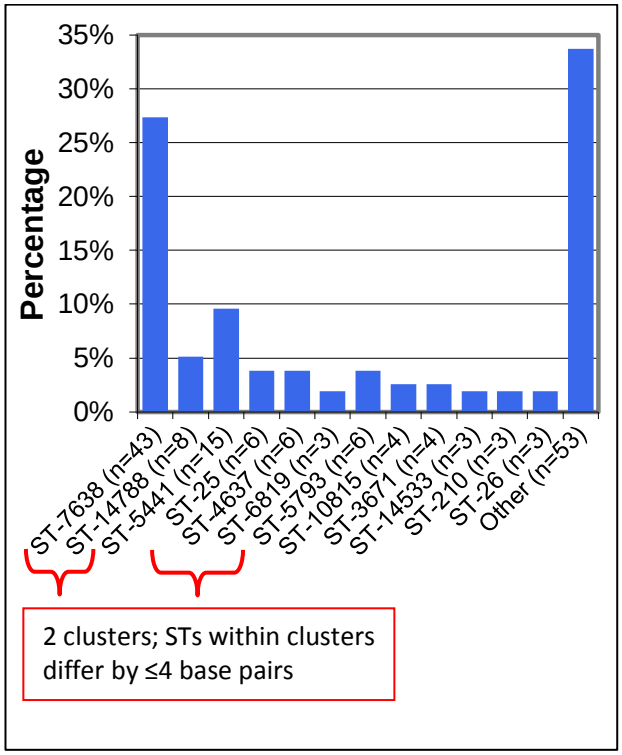
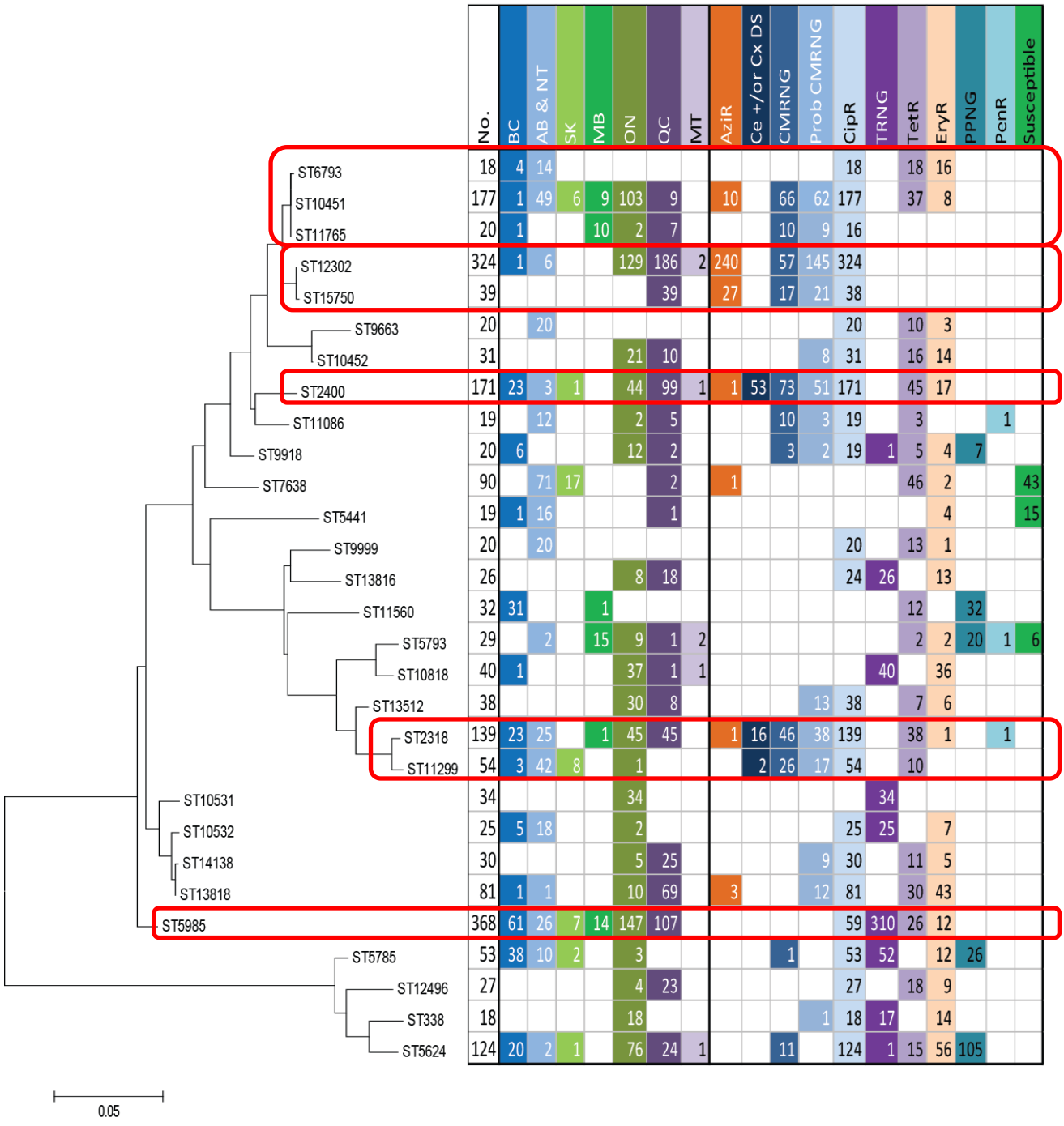


Figure 21d. Susceptible[b] Isolates, N=157[c]



[a]Other sequence types of Azithromycin resistant isolates contain 1 isolate each
[b]Susceptible isolates are isolates that were tested at the NML and not resistant to any of the antibiotics tested.
[c]Other sequence types of Susceptible isolates contain 1 or 2 isolates each.

Figure 22. Genetic Relationship of Prevalent *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2016[ab]



[a] This tree represents the 29 most prevalent STs of 2016 with 2,086 isolates. The remaining 1,006 isolates are dispersed among 461 sequence types (STs) containing 1 to 17 isolates each.

[b] bp=nucleotide base pair

The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura-Nei model [Tamura, 1993]. The tree with the highest log likelihood (-4090.7953) 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 29 nucleotide sequences. Codon positions included were 1st+2nd+3rd+Noncoding. All positions containing gaps and missing data were eliminated. There were a total of 782 positions in the final dataset. Evolutionary analyses were conducted in MEGA6 [Tamura, 2013].

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 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. 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 2010 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 2011, 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, 2011). The United States (CDC, 2012) and Europe (Bignell, 2013) also updated treatment recommendations to combination therapy with intramuscular ceftriaxone and oral azithromycin. Since the 2011 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≥0.25 mg/L for cefixime and ≥0.125 mg/L for ceftriaxone), decreased susceptibility to cefixime declined from 2.2% (68/3,036) in 2012 to 0.3% (14/4,538) in 2016. Decreased susceptibility to ceftriaxone also declined from 5.5% (168/3,036) in 2012 to 1.8% (80/4,538) in 2016.

Similarly, the US reported a decline in decreased susceptibility to cefixime from 1.4% in 2011 to 0.5% in 2015. Decreased susceptibility to ceftriaxone declined from 0.4% in 2011 to 0.3% in 2015 (CDC, 2016). The UK reported that the prevalence of isolates with decreased cefixime susceptibility dropped from 6.3% in 2010 to 0.4% in 2015. Decreased susceptibility to ceftriaxone declined from 0.2% in 2012 to 0% in 2015 (Public Health England, 2016). Using 0.06 mg/L and 0.125 mg/L as decreased susceptibility breakpoints, Australia reported 5.4% decreased susceptibility to ceftriaxone in 2014 which had decreased from 8.8% in 2013 (Lahra, 2015). Only 0.6% of isolates in Australia had ceftriaxone MICs of 0.125 mg/L in 2014, and there were no isolates with higher MICs (Lahra, 2015). The decline in decreased susceptibility to cephalosporins is encouraging, however, in 2017, routine surveillance identified the first ceftriaxone resistant *N. gonorrhoeae* in Canada (Lefebvre, 2018). 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 increase and in 2016, 7.2% of all isolates tested were azithromycin resistant. This percentage included 240 isolates with ST-12302 which, in addition to showing resistance to azithromycin and erythromycin, are resistant to other antimicrobials including ciprofloxacin, tetracycline

and penicillin. The proportion that are resistant exceeds the 5% level at which an antimicrobial should be reviewed as an appropriate treatment, according to the WHO (2012). In Canada, the level of azithromycin resistance levels exceeded that in the US, which was reported as 2.6% in 2015 (CDC, 2016). The UK reported an increase in azithromycin resistance (MIC≥1 mg/L) from 1.0% in 2014 to 9.8% in 2015, possibly due in part to a change in media being used. Also, only 9% of these isolates had an MIC≥2 mg/L (Public Health England, 2016). Australia reported a slight increase in azithromycin resistance from 2.1% in 2013 to 2.5% in 2014 (Lahra, 2015).

In 2016, Canada identified 1 azithromycin resistant isolate with decreased susceptibility to cefixime and ceftriaxone. The US did not identify any isolates with this antimicrobial profile. The UK reported the world's first treatment failure to dual ceftriaxone (MIC=0.25 mg/L) and azithromycin (MIC=1.0 mg/L) therapy in 2015 (Fifer, 2017).

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.

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, 2012 – 2016[a]**

Province	2012 GC Cultures			2013 GC Cultures			2014 GC Cultures			2015 GC Cultures			2016 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	372	92	24.70%	454	170	37.40%	492	336	68.29%	602	387	64.29%	600	348	58.00%
Alberta	497	94	18.90%	514	134	26.10%	468	339	72.44%	793	514	64.82%	786	544	69.21%
Saskatchewan	57	57	100%	69	67	97.10%	91	91	100%	62	64	100%	86	85	99.00%
Manitoba	49	8	16.30%	29	7	24.10%	46	46	100%	48	45	93.75%	85	82	96.47%
Ontario	1,218	403	33.10%	1404	498	35.50%	1767	855	48.39%	1,673	1,075	64.26%	1,735	1,068	61.56%
Québec	838	390	46.50%	716	298	41.60%	918	408	44.44%	986	528	53.55%	1,197	927	77.44%
New Brunswick	3	3	100%	5	5	100%	3	3	100%	10	8	80%	6	3	50.00%
Nova Scotia	0	0	na	1	1	100%	15	14	93.33%	13	15	100%	32	31	97.00%
Newfoundland	1	0	0%	1	1	100%	9	9	100%	1	1	100%	0	0	na
Prince Edward Island	1	1	100%	2	2	100%	0	0	na	1	1	100%	0	0	na
Northwest Territories	0	0	na	0	0	na	0	0	na	1	1	100%	11	4	36.00%
Totals	**3,036**	**1,048**	**34.50%**	**3,195**	**1,183**	**37.00%**	**3,809**	**2,101**	**55.16%**	**4,190**	**2,639**	**62.98%**	**4,538**	**3,092**	**68.14%**

[a]No *Neisseria gonorrhoeae* cultures were reported to the NML or received from Nunavut or the Yukon in 2012 to 2016.

[b]Not including duplicates or isolates that were contaminated or did not grow for the NML.

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