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National Surveillance of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Annual Summary 2013

Streptococcus and STI Unit
Bacteriology and Enteric Diseases Program
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 the Northwest Territories, 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 2009-2013.
- The Canadian reported rate of gonorrhoea is on the rise and has more than doubled from 14.9 per 100,000 in 1997 to 36.2 per 100,000 in 2012. Gonorrhoea is the second most commonly reported bacterial sexually transmitted infection in Canada with 12,561 cases reported in 2012.
- 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 2013, a total of 3,195 *N. gonorrhoeae* isolates were cultured in public health laboratories across Canada; 1,183 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.
- In Canada, the increasing minimum inhibitory concentrations (MICs) to the 3rd generation cephalosporins are of concern. Modal MICs to cefixime increased from 0.032 mg/L in 2008 to 0.125 mg/L in 2010 but then decreased to 0.063 mg/L in 2013. Modal MICs to ceftriaxone increased from 0.032 mg/L in 2008 to 0.063 mg/L from 2009 to 2013.
- Using the WHO breakpoints of decreased susceptibility to cefixime at MIC≥0.25 mg/L and decreased susceptibility to ceftriaxone at MIC≥0.125 mg/L (WHO, 2012), the percentage of isolates with decreased susceptibility to ceftriaxone and/or cefixime was 3.9% (124/3,195) in 2013. This number represents a decrease from 5.9% (179/3,036) in 2012 and 7.6% (254/3,360) in 2011.
- Isolates with decreased susceptibility to cefixime have declined from a high of 4.2% (140/3,360) in 2011 to 1.8% (56/3,195) in 2013. Isolates with decreased susceptibility to ceftriaxone have declined from a high of 7.3% (218/2,970) in 2010 to 3.5% (112/3,195) in 2013.
- The proportion of azithromycin resistant (MIC ≥2 mg/L) *N. gonorrhoeae* isolates increased from 0.4% (11/3,106) in 2009 to 1.2% (37/3,195) in 2013.
- The proportion of ciprofloxacin resistant *N. gonorrhoeae* increased from 1.3% (59/4,458) in 2000 to a high of 36.0% (1,068/2,970) in 2010, subsequently decreasing to 29.3% (937/3,195) in 2013.
- In 2013, 24.3% (777/3,195) of the isolates were resistant to erythromycin; 18.9% (605/3,195) were resistant to penicillin; 33.0% (1054/3,195) were resistant to tetracycline.
- The NML began testing ertapenem and gentamicin in 2012. In 2012, the modal MIC for ertapenem was 0.063 mg/L which increased to 0.125 mg/L in 2013. The gentamicin modal MIC was 8 mg/L in 2012 and 2013.
- Since 2010, 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 2013, 294 different sequence types (STs) were identified among the 1,183 isolates tested and the most common sequence types were ST-2400, ST-9663 and ST-5985 at 12.1%, 7.4% and 6.1%, respectively.

INTRODUCTION

Neisseria gonorrhoeae is the causative agent of gonorrhoea and is the second most commonly reported bacterial sexually transmitted infection in Canada, with 12,561 cases reported in 2012 (Public Health Agency of Canada, 2014). Rates of reported cases of gonorrhoea have more than doubled from 14.9 cases per 100,000 population in 1997 to 36.2 cases per 100,000 population in 2012 (Public Health Agency of Canada, 2014). Globally, gonorrhoea is a public health threat with an estimated 106 million cases each year (World Health Organization, 2012). 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 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 gonorrhoea 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, 2008; World Health Organization, 2011) and reports of treatment failures in Canada (Allen, 2013) and around the world raises the possibility of gonorrhea infections becoming untreatable in the future. Azithromycin resistant isolates have also been identified. 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 now been identified in Canada. In response to the increasing MICs and reports of cefixime treatment failures, the Canadian Sexually Transmitted Infection (STI) Guidelines regarding gonorrhoea treatment have been updated to a combination therapy with 250 mg ceftriaxone intramuscularly and azithromycin 1 g orally as a first-line treatment for uncomplicated anogenital and pharyngeal infection in adults. Additional information on the treatment of gonococcal infection is available at http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/assets/pdf/section-5-6-eng.pdf.

A further challenge to the laboratories monitoring antimicrobial susceptibilities of gonorrhoea 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 gonorrhoea (Figure 1). This is of concern as *N. gonorrhoeae* cultures are required for antimicrobial susceptibility testing and some jurisdictions in Canada no longer maintain the capacity to culture this organism. In fact, over 70% of gonococcal infections in Canada are now diagnosed using NAAT and therefore antimicrobial susceptibility data in these jurisdictions are not available.

To make improvements to the current surveillance program, the enhanced surveillance of antimicrobial resistant *N. gonorrhoeae* (ESAG) study will begin in 2014. This sentinel public health practice and surveillance study for *N. gonorrhoeae* will collect 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 the treatment failure rate associated with regimens recommended by the Canadian STI Guidelines. Both antimicrobial susceptible and resistant strains of gonorrhoea will be 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 1985; these results inform the gonococcal infection treatment recommendations in the Canadian Guidelines on Sexually Transmitted Infections.

METHODS

In 2013, provincial public health laboratories submitted a total of 1,183 viable *N. gonorrhoeae* isolates to the NML for antimicrobial susceptibility testing as part of the passive National *Neisseria gonorrhoeae* Surveillance Program (Table 1). These data are provided to indicate 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. 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).

N. gonorrhoeae isolates are submitted to the NML 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. Therefore, the total number of isolates cultured in all provinces was used as the denominator to calculate resistance proportion. To standardize the susceptibility testing between laboratories, proficiency surveys were conducted semi-annually. Minimum inhibitory concentration, or MIC (the minimum concentration of antibiotic which will inhibit the growth of the organism) was performed using agar dilution, and interpretations were based on the criteria outlined in Table 2. Resistance characterization definitions are provided in Table 3. Isolates were also characterized by plasmid profiles analysis, production of β-lactamase and the presence of *tetM* determinant.

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. Number of *Neisseria gonorrhoeae* Culture Isolates Tested at the NML by Province, 2009-2013[ab]

Province	2009	2010	2011	2012	2013	Total
British Columbia	183	256	176	92	170	877
Alberta	91	164	156	94	136	641
Saskatchewan	30	11	35	57	67	200
Manitoba	3	11	12	8	7	41
Ontario	383	383	428	403	498	2,095
Québec	216	335	282	390	301	1,524
New Brunswick	4	9	6	3	5	27
Nova Scotia	2	69	77	0	1	149
Newfoundland	2	7	0	0	1	10
Prince Edward Island	0	0	0	1	2	3
Total isolates received at NML	914	1,245	1,172	1,048	1,188	5,567
Total viable isolates available for testing	913	1,233	1,158	1,031	1,183	5,518
Total isolates resistant to at least one antibiotic	873	1,137	1,075	987	1,153	5,225
Total number of isolates tested in each province[a]	3,106	2,970	3,360	3,036	3,195	15,667
Percentage of isolates resistant to at least one antibiotic	28.1%	38.3%	32.0%	32.5%	36.1%	33.4%
Percentage of total cases tested	27.8%	26.1%	29.5%	24.2%	26.6%[b]	26.8%
Total cases reported in Canada	**11,178**	**11,397**	**11,394**	**12,561**	**12,000[b]**	**58,530**

[a]Total number of isolates tested by the provincial laboratories is used as the denominator in all % resistance calculations.
[b]2013 number of cases reported and percentage of total cases tested are estimated.

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 #P 7794
Tetracycline	0.064 – 64.0	≤ 0.25		0.5 - 1.0	≥ 2.0	Sigma #T 3383
Erythromycin	0.032 – 32.0	≤ 1.0			≥ 2.0	Sigma #E 5389
Spectinomycin	4.0 – 256.0	≤ 32.0		64	≥ 128.0	Sigma #S 9007
Ciprofloxacin	0.001 – 64.0	≤ 0.06		0.12 - 0.5	≥ 1.0	Bayer Health Care
Ceftriaxone	0.001 – 2.0	≤ 0.25	≥ 0.125			Sigma #C 5793
Cefixime	0.002 – 2.0	≤ 0.25	≥ 0.25			Wyeth - Ayerst
Azithromycin	0.016 – 32.0	≤ 1.0			≥ 2.0	Pfizer
Ertapenem	0.002 - 2.0	Interpretive Standards Not Available				Sequoia SRP01333e
Gentamicin	0.5 - 128	Interpretive Standards Not Available				MP Biomedicals

[a]MIC Interpretative standards as recommended by the Clinical and Laboratory Standards Institute (CLSI, 2014) except for erythromycin (Ehret, 1996) and azithromycin (Centres for Disease Control and Prevention, 2007) and ceftriaxone and cefixime (World Health Organization, 2012).
[b]S= Susceptible, I=Intermediate, R= Resistant, DS= Decreased susceptibility

Table 3. *Neisseria gonorrhoeae* Antimicrobial Resistance Characterization Definitions

Characterization	Description	Definition
PPNG	Penicillinase Producing *Neisseria gonorrhoeae*	Pen MIC ≥ 2.0 mg/L, β-lactamase positive, β-lactamase plasmid (3.05, 3.2 or 4.5 Mdal plasmid)
TRNG	Tetracycline Resistant *Neisseria gonorrhoeae*	Tet MIC ≥ 16.0 mg/L, 25.2 Mdal plasmid, 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 R ≥ 128 mg/L
CxDS	*Neisseria gonorrhoeae* with Decreased Susceptiblity to Ceftriaxone	Cx MIC ≥ 0.125 mg/L
CeDS	*Neisseria gonorrhoeae* with Decreased Susceptiblity to Cefixime	Ce MIC ≥ 0.25 mg/L

RESULTS AND DISCUSSION

In 2013, a total of 3,195 *N. gonorrhoeae* isolates were cultured in public health laboratories across Canada; 1,183 of these were submitted to the NML and found viable for antimicrobial susceptibility testing. A total of 1,153 were found to be resistant to at least one antibiotic tested; this translates to 36.1% of all *N. gonorrhoeae* cases diagnosed by culture as carrying antimicrobial resistance (1,153/3,195) (Figure 1). The characterization of each resistant *N. gonorrhoeae* isolate is provided in Appendix B. Of all the gonorrhoea cases reported in 2013 (approximated at over 12,000 cases), over 70% were diagnosed by NAAT for which there is no antimicrobial susceptibility data.

Gender and age data was available for 99.5% (1,177/1,183) of isolates tested at the NML (Table 4). Of these, 83.1% (978/1,177) were males ranging from 1 month to 74 years of age. A total of 16.9% (199/1,177) of isolates were from females aging 2 to 71 years.

Anatomic source data was available for 74.5% (881/1,183) of the isolates sent to the NML (Table 5). Of these, 56.4% (497/881) were urethral, 21.1% (186/881) were rectal, 9.8% (86/881) were from the throat, 6.8% (60/881) were cervical, 4.1% (36/881) were vaginal and 1.8% (16/881) were from other sources.

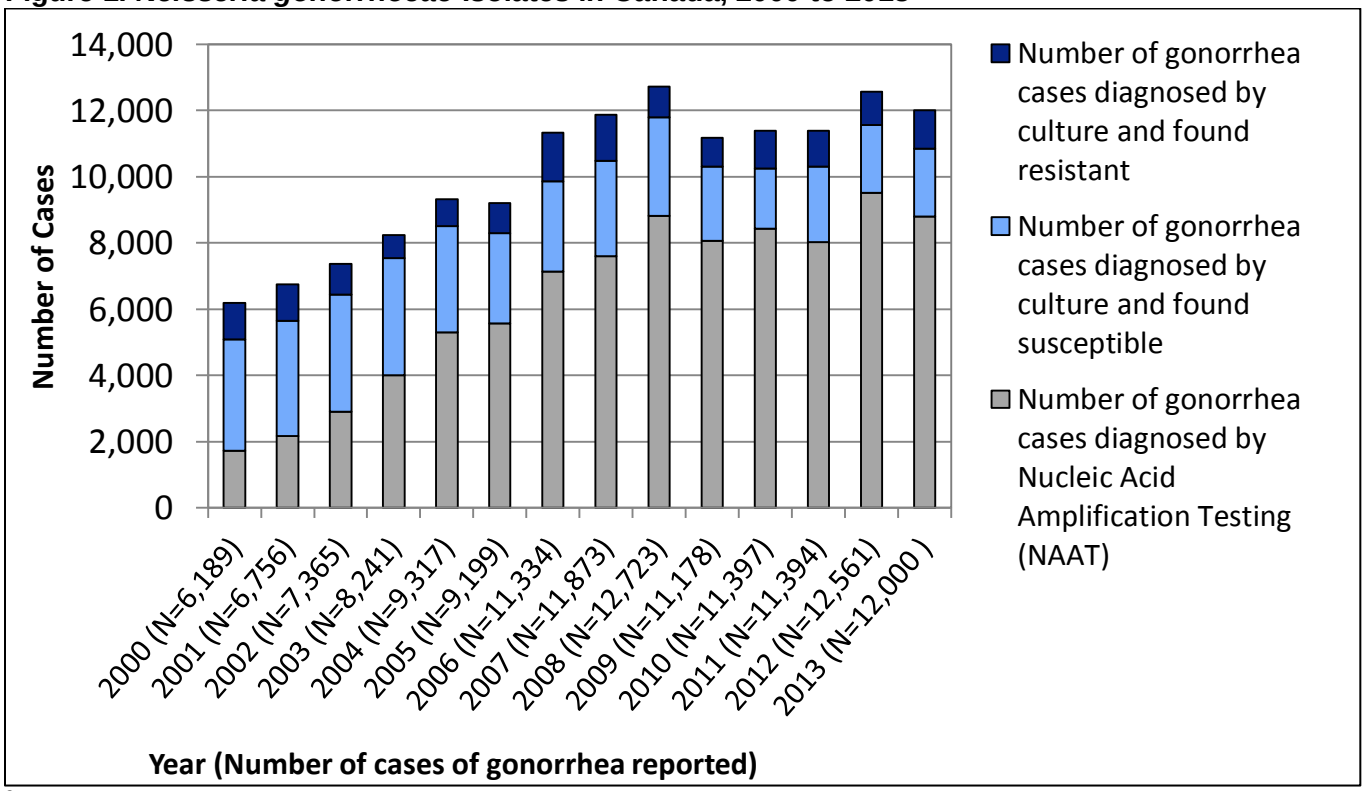
Table 4. Demographic Data for the *Neisseria gonorrhoeae* isolates tested at the NML, 2013 (N=1,183)

Age	Male	Female	Not Specified	Totals
Under 15	3	8	0	11
15 - 20	89	53	0	142
21 - 25	224	50	2	276
26 - 35	383	50	1	434
36 - 45	143	21	0	164
46 - 55	99	12	0	111
56 - 65	29	4	0	33
65 +	8	1	0	9
Not Specified	0	0	3	3
Total	**978**	**199**	**6**	**1,183**

Table 5. Anatomic Isolation Sites for the *Neisseria gonorrhoeae* isolates tested at the NML, 2013 (N=1,183)

Isolation Site	Male	Female	Not Specified	Totals
Penis/ Urethra	497	0	0	497
Rectum	180	4	2	186
Throat	71	14	1	86
Cervix	0	60	0	60
Vagina	0	36	0	36
Other	11	5	0	16
Not Specified	219	80	3	302
Total	**978**	**199**	**6**	**1,183**

Figure 1. *Neisseria gonorrhoeae* Isolates in Canada, 2000 to 2013[a]

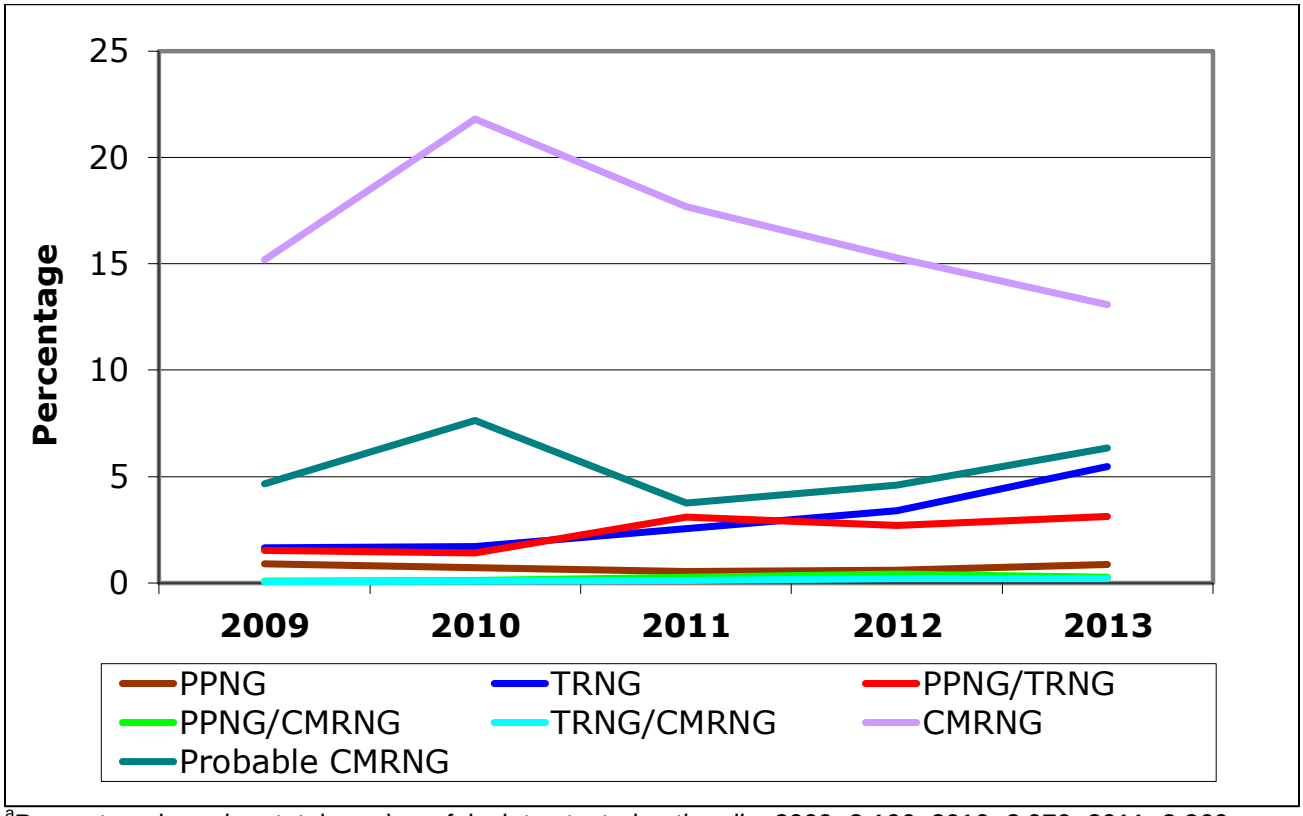


[a]number of gonorrhea cases reported in 2013 is estimated

TRENDS IN ANTIMICROBIAL SENSITIVIES

In 2013, 13.5% (432/3,195) of isolates were classified as Chromosomal Mediated Resistant *Neisseria gonorrhoeae* (CMRNG), while the plasmid-mediated resistant strains occurred at lower rates. Penicillinase Producing *Neisseria gonorrhoeae* (PPNG) accounted for 4.3% (136/3,195) and Tetracycline Resistant *Neisseria gonorrhoeae* (TRNG) for 8.8% (281/3,195) of isolates (Figure 2).

Figure 2. Trends of PPNG, TRNG, CMRNG, Probable CMRNG *Neisseria gonorrhoeae* in Canada from 2009 to 2013[a]



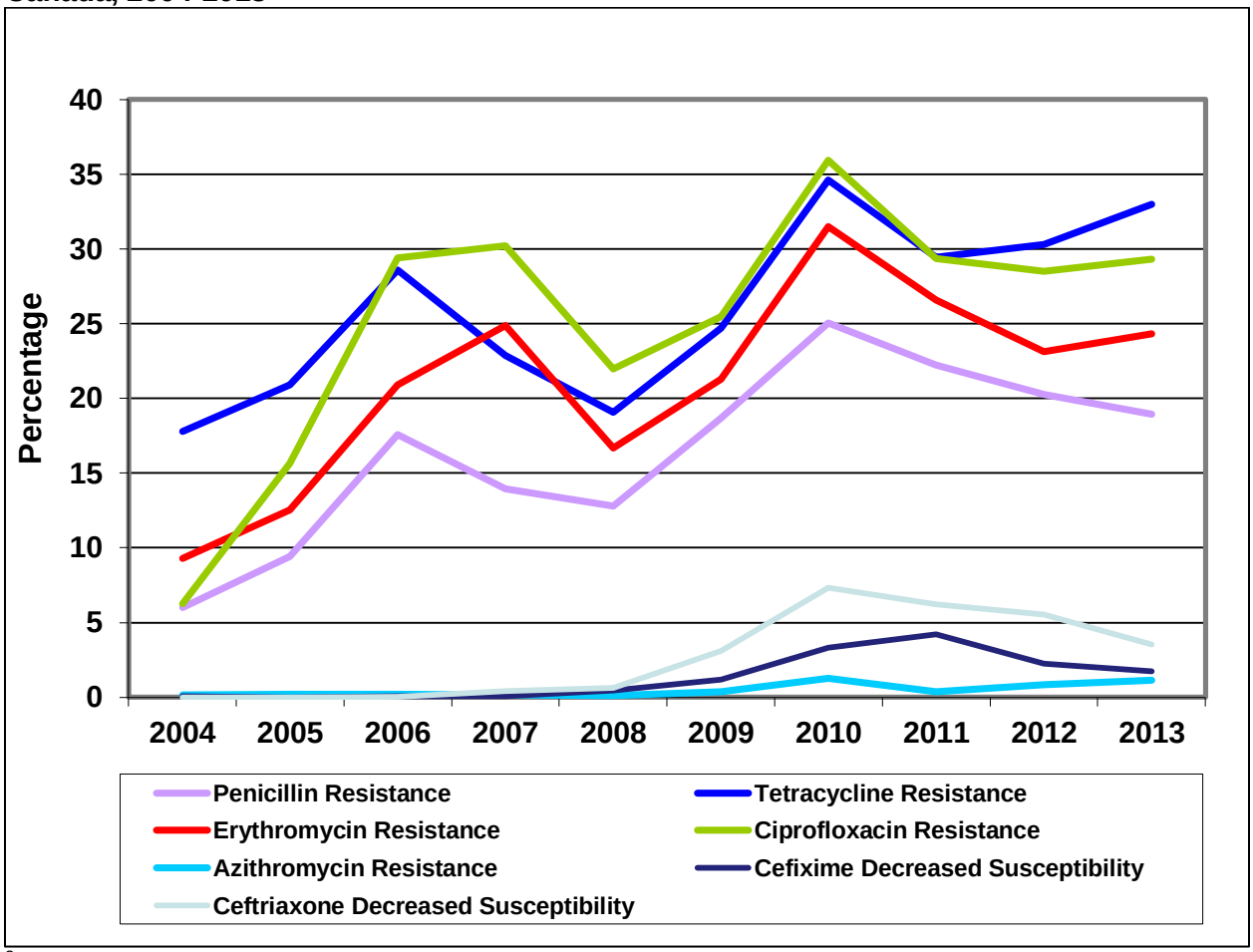
[a]Percentage based on total number of isolates tested nationally: 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195

Figure 3 shows the trends of antimicrobial susceptibilities of *N. gonorrhoeae* tested in Canada from 2004 to 2013. In 2004, only 9.3% (373/4,018) of Canadian isolates were found to be erythromycin resistant. This percentage increased to 31.5%, (936/2,970) by 2010 but then decreased to 24.3% (777/3,195) by 2013

Penicillin resistance increased from 6.0% (242/4,018) in 2004, to 25.1% (744/2,970) in 2010 and then decreased to 18.9% (605/3,195) in 2013.

Tetracycline resistance increased from 17.8% (715/4,018) in 2004 to 34.6% (1,028/2,970) in 2010. It decreased to 33.0% (1054/3,195) in 2013. Of the 5,518 viable isolates tested at NML between 2009 and 2013, none showed resistance to spectinomycin.

Figure 3. Trends of Antimicrobial Susceptibilities of *Neisseria gonorrhoeae* Tested in Canada, 2004-2013[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

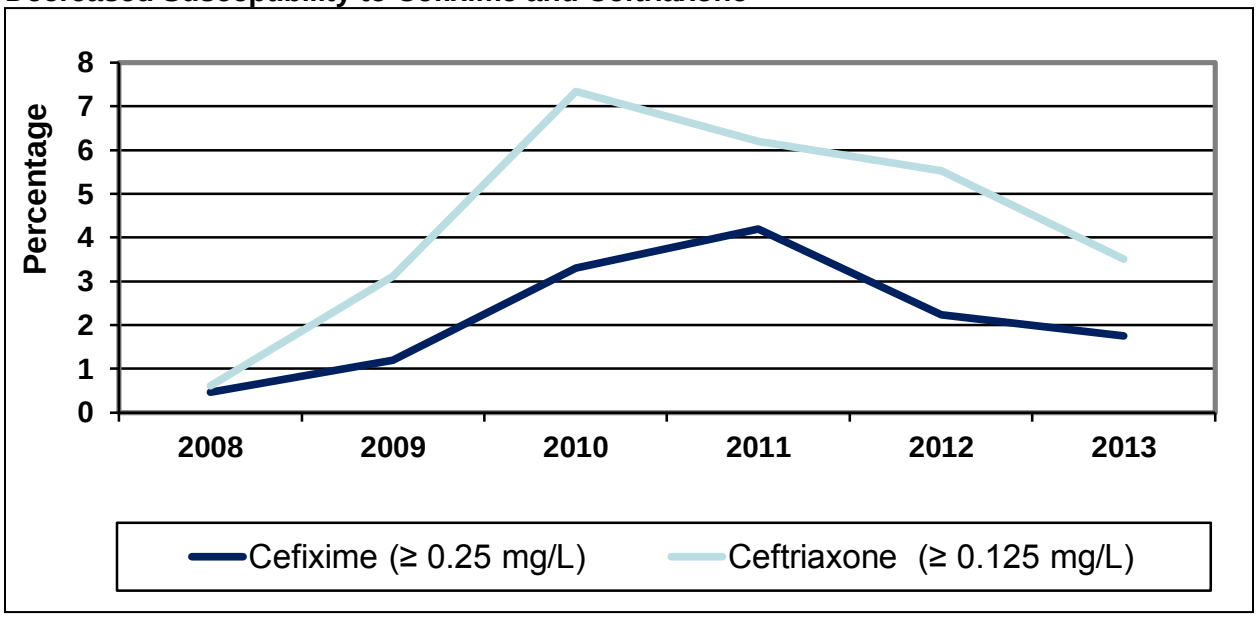
THIRD GENERATION CEPHALOSPORINS

In 2013, according to WHO (2012) definitions (isolates with MICs ≥0.25 mg/L for cefixime and ≥0.125 mg/L for ceftriaxone have decreased susceptibility), 1.8% of isolates (56/3,195) were identified as having decreased susceptibility to cefixime and 3.5% (112/3,195) were identified as having decreased susceptibility to ceftriaxone. These rates are higher than they were in 2008 [0.5% (18/3,907) and 0.6% (24/3,907), respectively] but lower than in 2011 [4.2% (140/3,360) and 6.2% (208/3,360), respectively] (Figure 4).

In 2013, 3.9% of isolates (124/3,195) were identified with decreased susceptibility to ceftriaxone and/or cefixime decreasing from 5.9% in 2012 (179/3,036) and 7.6% in 2011 (254/3,360).

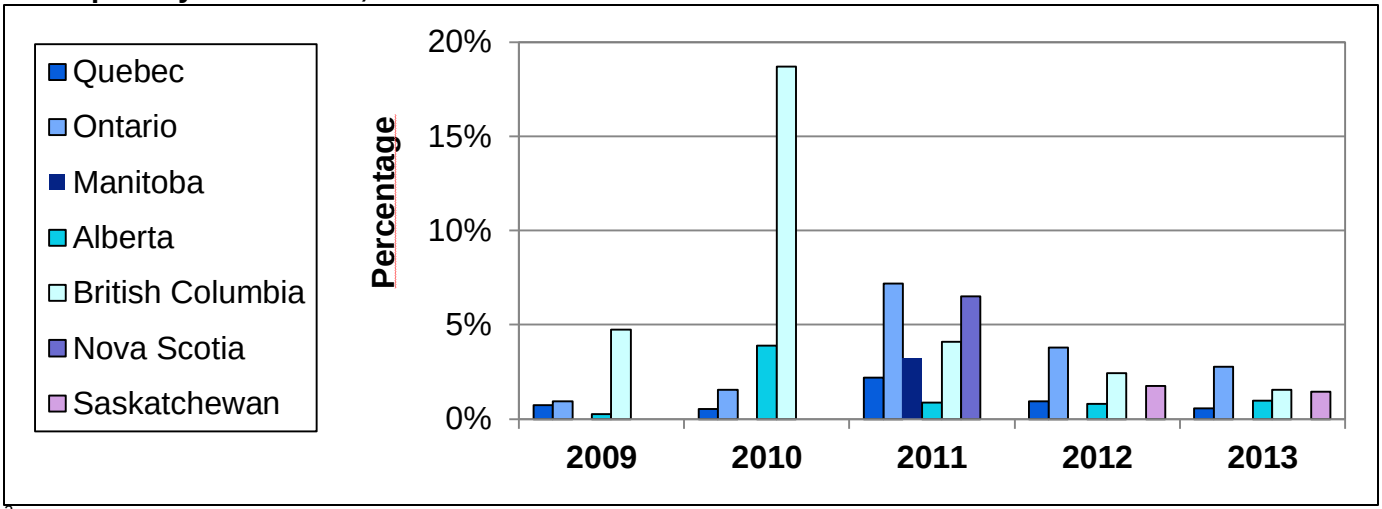
The geographical distribution of *N. gonorrhoeae* isolates with decreased susceptibility to cefixime and ceftriaxone within Canada are represented in Figures 5 and 6 and in Tables 6 and 7.

Figure 4. *Neisseria gonorrhoeae* Isolates Received by the NML between 2008 and 2013 with Decreased Susceptibility to Cefixime and Ceftriaxone[a]



[a]Percentage 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

Figure 5. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Cefixime, 2009 to 2013[a]



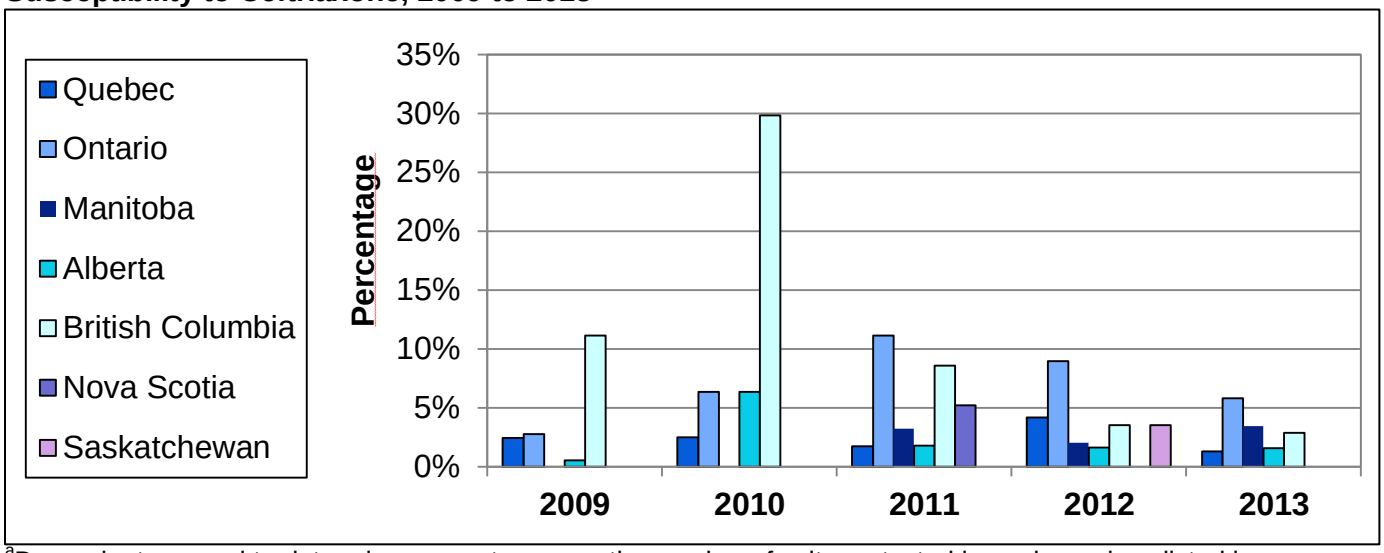
[a]Denominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 6. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Cefixime, 2009 to 2013[a]

Province	Year				
	2009	2010	2011	2012	2013
Quebec	7	6	23	8	4
Ontario	13	17	87	46	39
Manitoba	0	0	1	0	0
Alberta	1	11	4	4	5
British Columbia	14	64	20	9	7
Nova Scotia	0	0	5	0	0
Saskatchewan	0	0	0	1	1
Total No. of isolates	**35**	**98**	**140**	**68**	**56**
% CeDS of all isolates tested nationally	**1.1%**	**3.3%**	**4.2%**	**2.2%**	**1.8%**

[a]Percentage based on total number of isolates tested nationally: 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195

Figure 6. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Ceftriaxone, 2009 to 2013[a]



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

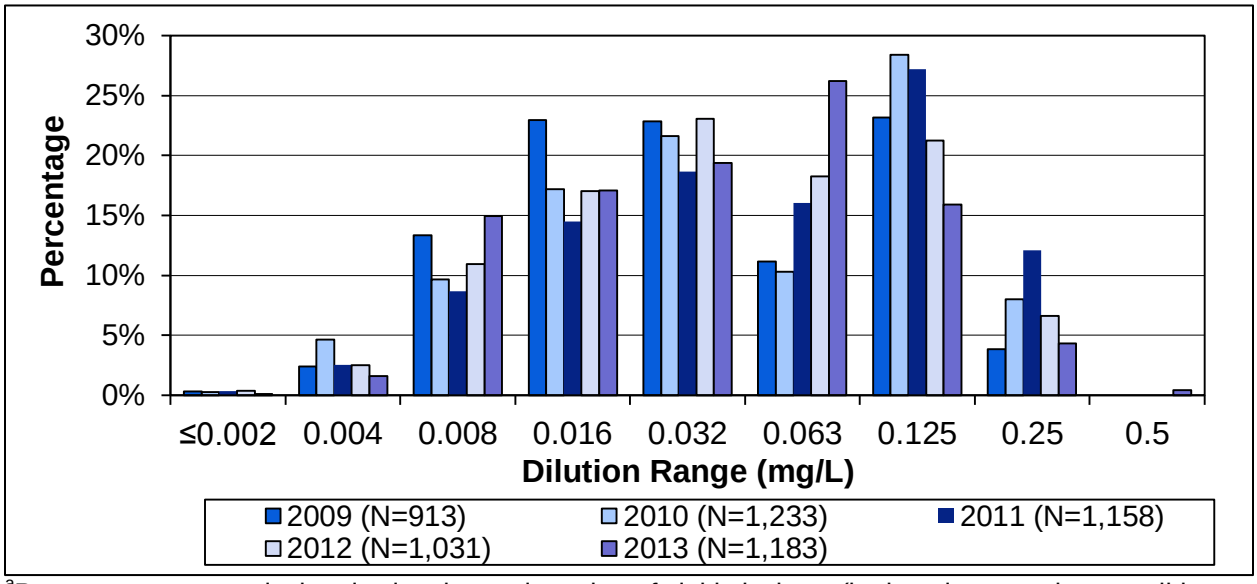
Table 7. Geographical Distribution of *Neisseria gonorrhoeae* Isolates with Decreased Susceptibility to Ceftriaxone, 2009 to 2013[a]

Province	Year				
	2009	2010	2011	2012	2013
Quebec	23	27	18	35	9
Ontario	38	70	135	109	81
Manitoba	0	1	1	1	1
Alberta	2	18	8	8	8
British Columbia	33	102	42	13	13
Nova Scotia	0	0	4	0	0
Saskatchewan	0	0	0	2	0
Total No. of isolates	**96**	**218**	**208**	**168**	**112**
% CxDS of all isolates tested nationally	**3.1%**	**7.3%**	**6.2%**	**5.5%**	**3.5%**

[a]Percentage based on total number of isolates tested nationally: 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195

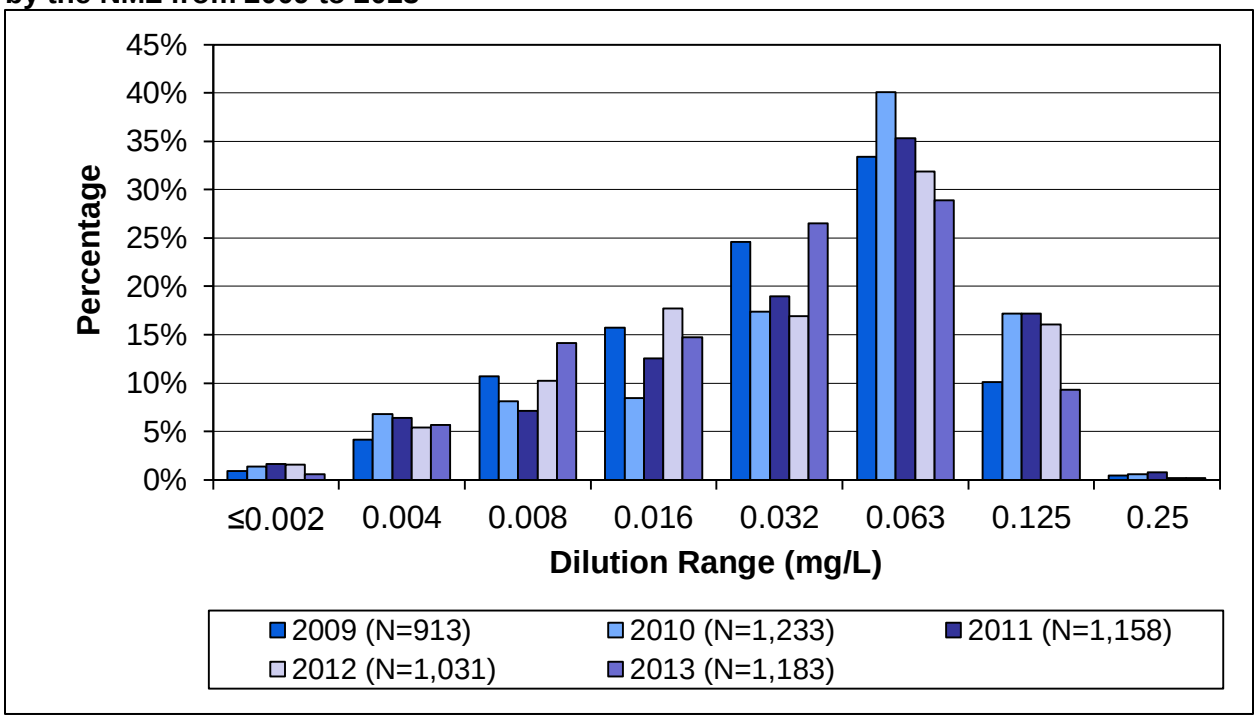
In 2009, 2010 and 2011 the modal MIC for cefixime was 0.125 mg/L decreasing to 0.032 mg/L in 2012 and increasing again to 0.063 in 2013. The ceftriaxone modal MIC has remained at 0.063 mg/L from 2009 thru 2013 (Figures 7-10, Tables 8 and 9).

Figure 7. Trends of Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[a]



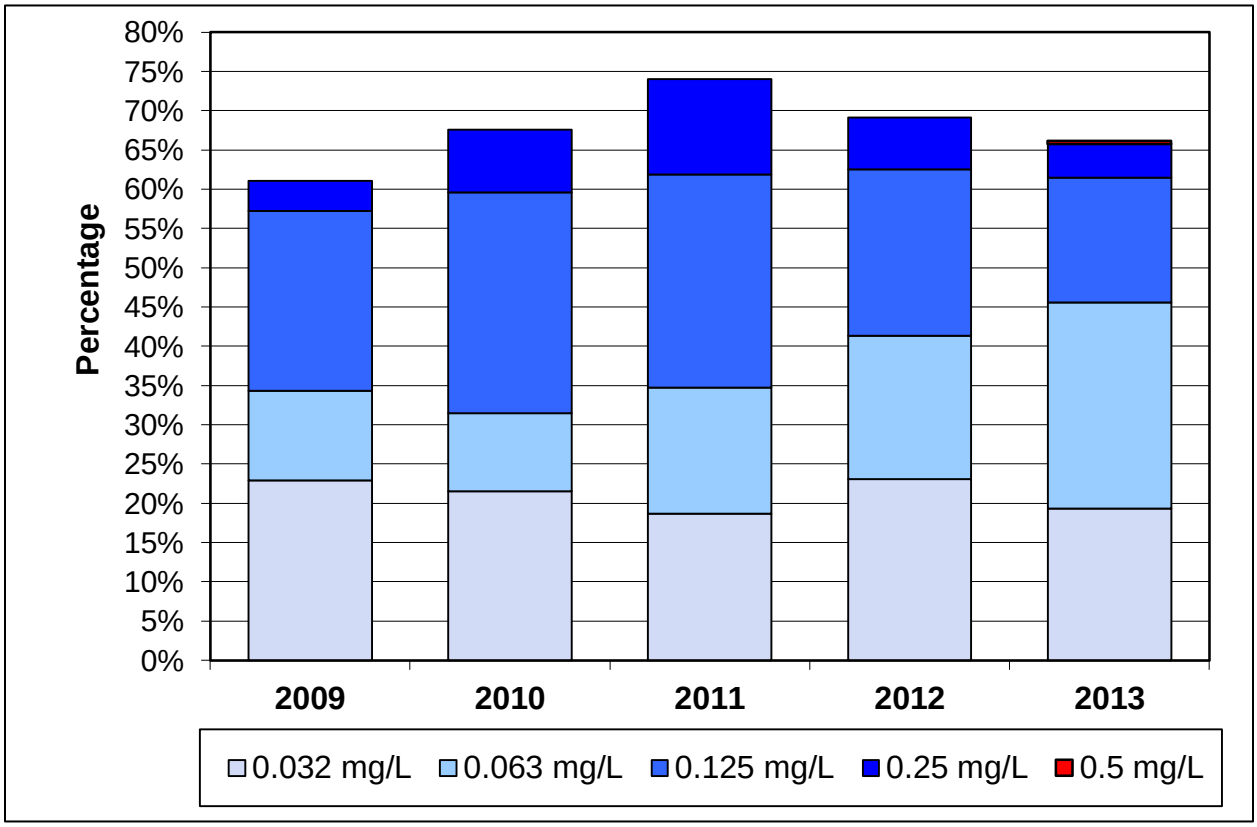
[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by NML as the denominator (N).

Figure 8. Trends of Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[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 9. Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[a]



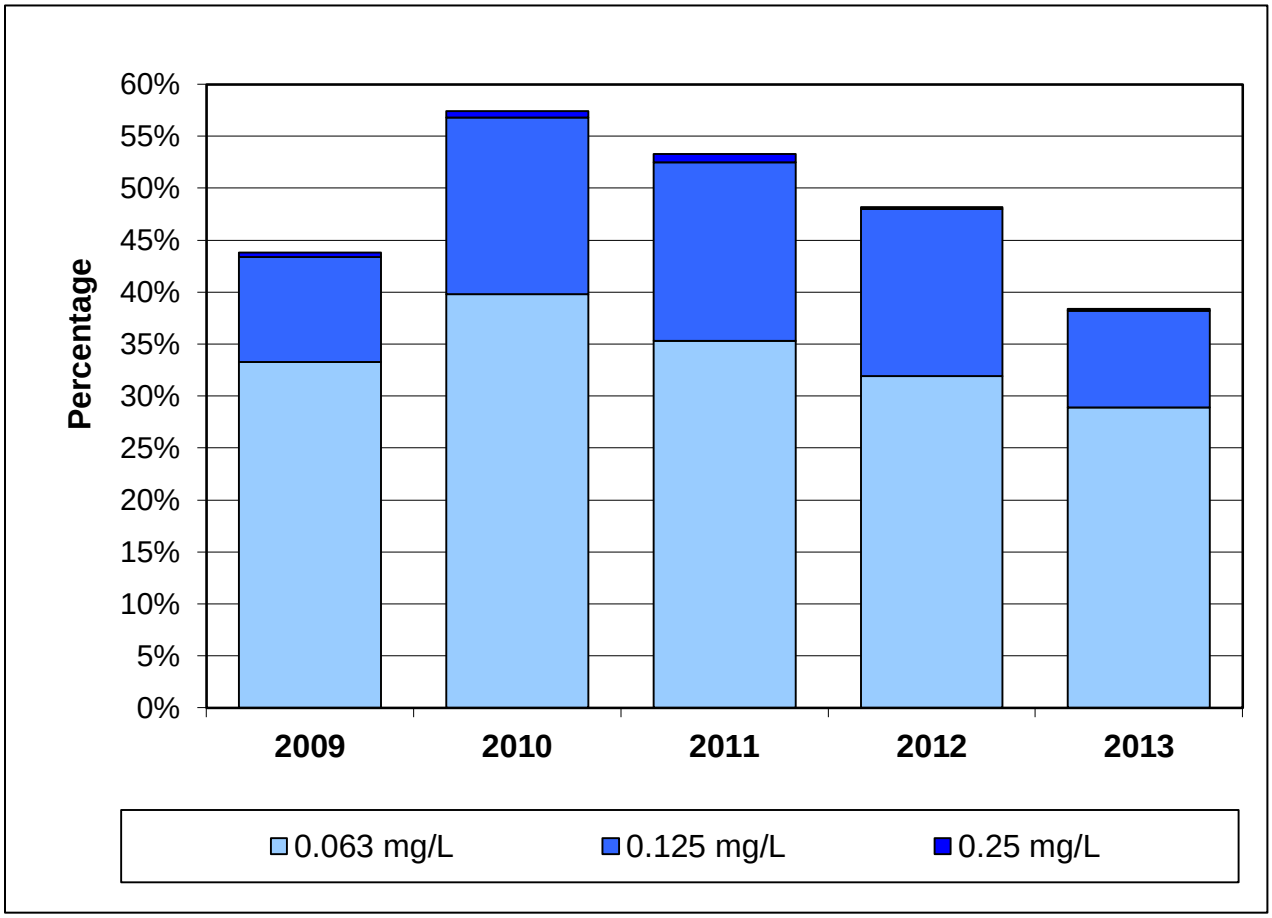
[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2009=913; 2010=1,233; 2011=1,158; 2012=1,031; 2013=1,183

Table 8. Cefixime Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[a]

Dilutions (mg/L)	Year				
	2009	2010	2011	2012	2013
0.032 mg/L	22.9%	21.5%	18.7%	23.1%	19.4%
0.063 mg/L	11.4%	10.0%	16.1%	18.2%	26.2%
0.125 mg/L	22.9%	28.1%	27.2%	21.2%	15.9%
0.25 mg/L	3.8%	8.0%	12.1%	6.6%	4.3%
0.5 mg/L	0.0%	0.0%	0.0%	0.0%	0.4%

[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2009=913; 2010=1,233; 2011=1,158; 2012=1,031; 2013=1,183

Figure 10. Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[a]



[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2009=913; 2010=1,233; 2011=1,158; 2012=1,031; 2013=1,183

Table 9. Ceftriaxone Susceptibilities of *Neisseria gonorrhoeae* Isolates received by the NML from 2009 to 2013[a]

Dilutions (mg/L)	Year				
	2009	2010	2011	2012	2013
0.063 mg/L	33.3%	39.8%	35.3%	31.9%	28.9%
0.125 mg/L	10.1%	17.0%	17.2%	16.1%	9.3%
0.25 mg/L	0.4%	0.6%	0.8%	0.2%	0.2%

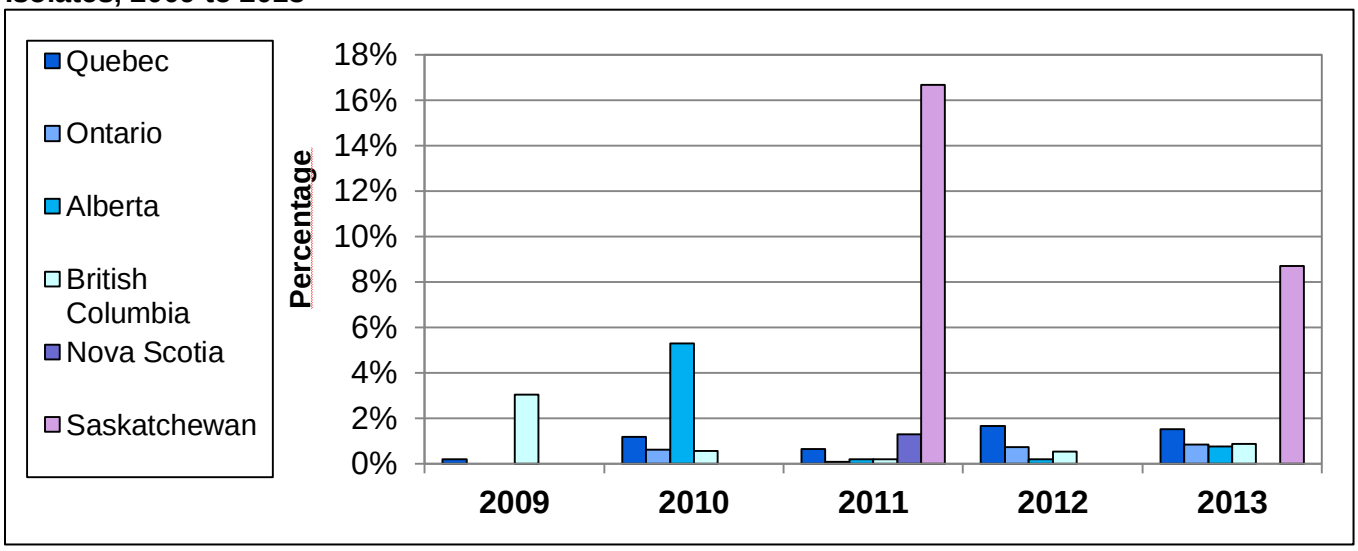
[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2009=913; 2010=1,233; 2011=1,158; 2012=1,031; 2013=1,183

AZITHROMYCIN

The distribution of azithromycin resistant isolates across Canada is represented in Figure 11 and Table 10. Azithromycin resistant *N. gonorrhoeae* increased from 0.4% (11/3,106) in 2009 to 1.2% (37/3,195) in 2013. Between 2009 and 2012, five isolates with high level azithromycin resistance (MIC ≥256 mg/L) were identified in Canada. The modal MIC for azithromycin has remained at 0.5 mg/L each year between 2009 and 2012. In 2013, the modal decreased to 0.25 mg/L (Figures 12 and 13 and Table 11).

In 2012, seven isolates with combined decreased susceptibility to cephalosporins and resistance to azithromycin were identified (0.2%, 7/3,036). In 2013, eight (0.3%, 8/3,195) of these isolates were identified (Table 12). These are the first isolates to emerge in Canada with both decreased susceptibility to cephalosporins and resistance to azithromycin thus threatening the success of currently recommended dual therapy treatment options.

Figure 11. Geographical Distribution of Azithromycin Resistant *Neisseria gonorrhoeae* Isolates, 2009 to 2013[a]



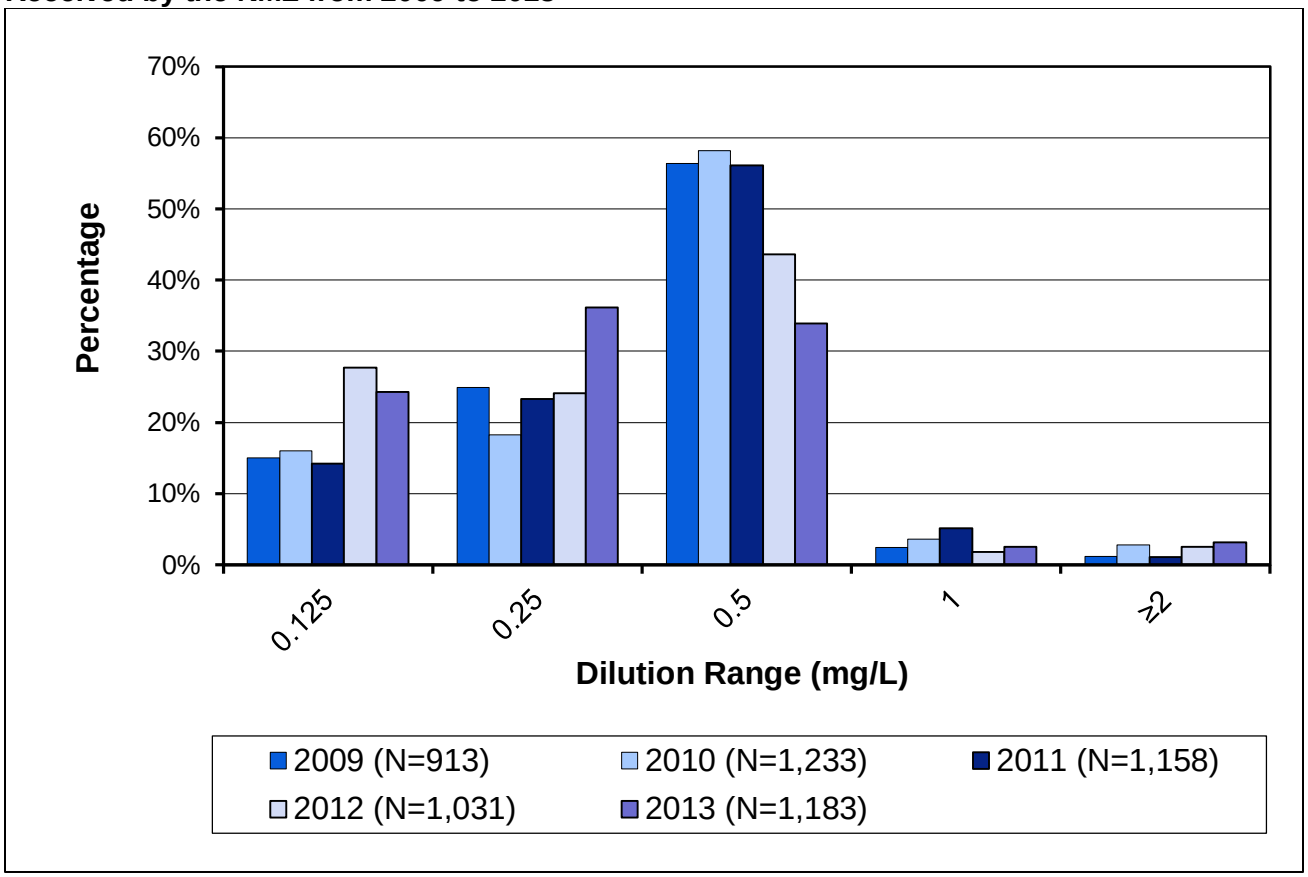
[a]Denominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 10. Geographical Distribution of Azithromycin Resistant *Neisseria gonorrhoeae* Isolates, 2009 to 2013[a]

Province	Year				
	2009	2010	2011	2012	2013
Quebec	2	13	7	14	11
Ontario	0	7	1	9	12
Alberta	0	15	1	1	4
British Columbia	9	2	1	2	4
Nova Scotia	0	0	1	0	0
Saskatchewan	0	0	2	0	6
Total No. of AzR isolates	11	37	13	26	37
% AzR of all isolates tested nationally	0.4%	1.3%	0.4%	0.9%	1.2%

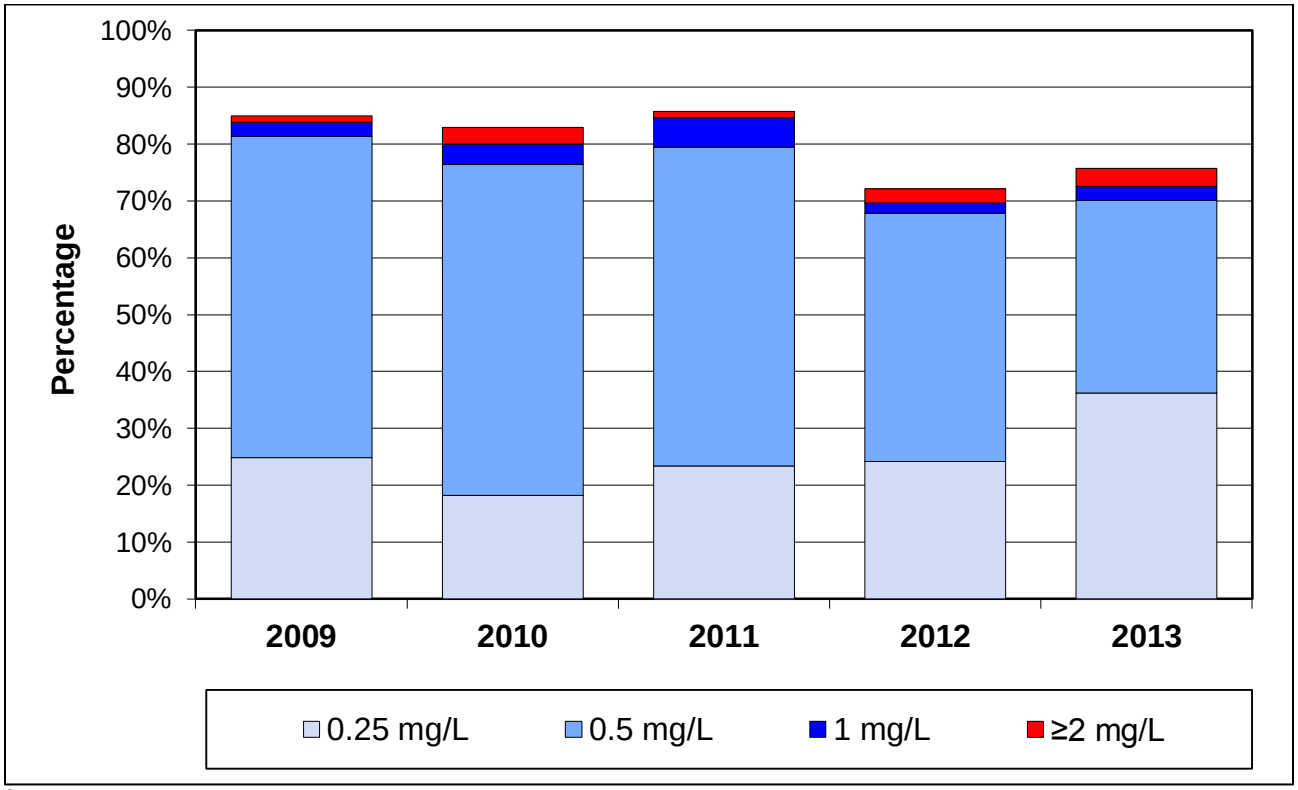
[a]Percentage based on total number of isolates tested nationally: 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195

Figure 12. Trends of Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[a]



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

Figure 13. Azithromycin Susceptibilities of *Neisseria gonorrhoeae* Isolates Received by the NML from 2009 to 2013[a]



[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2009=913; 2010=1,233; 2011=1,158; 2012=1,031; 2013=1,183

Table 11. Azithromycin Susceptibilities of Neisseria gonorrhoeae Isolates Received by the NML from 2009 to 2013[a]

Dilution (mg/L)	Year				
	2009	2010	2011	2012	2013
0.25 mg/L	24.9%	18.3%	23.3%	24.2%	36.2%
0.5 mg/L	56.5%	58.2%	56.1%	43.7%	33.9%
1 mg/L	2.4%	3.6%	5.2%	1.8%	2.5%
≥2 mg/L	1.2%	3.0%	1.1%	2.5%	3.1%

[a]Percentages were calculated using the total number of viable isolates (both resistant and susceptible isolates) tested by the NML as the denominator (N): 2009=913; 2010=1,233; 2011=1,158; 2012=1,031; 2013=1,183

Table 12. *Neisseria gonorrhoeae* isolates with combined decreased susceptibility to cephalosporins and resistance to azithromycin[a]

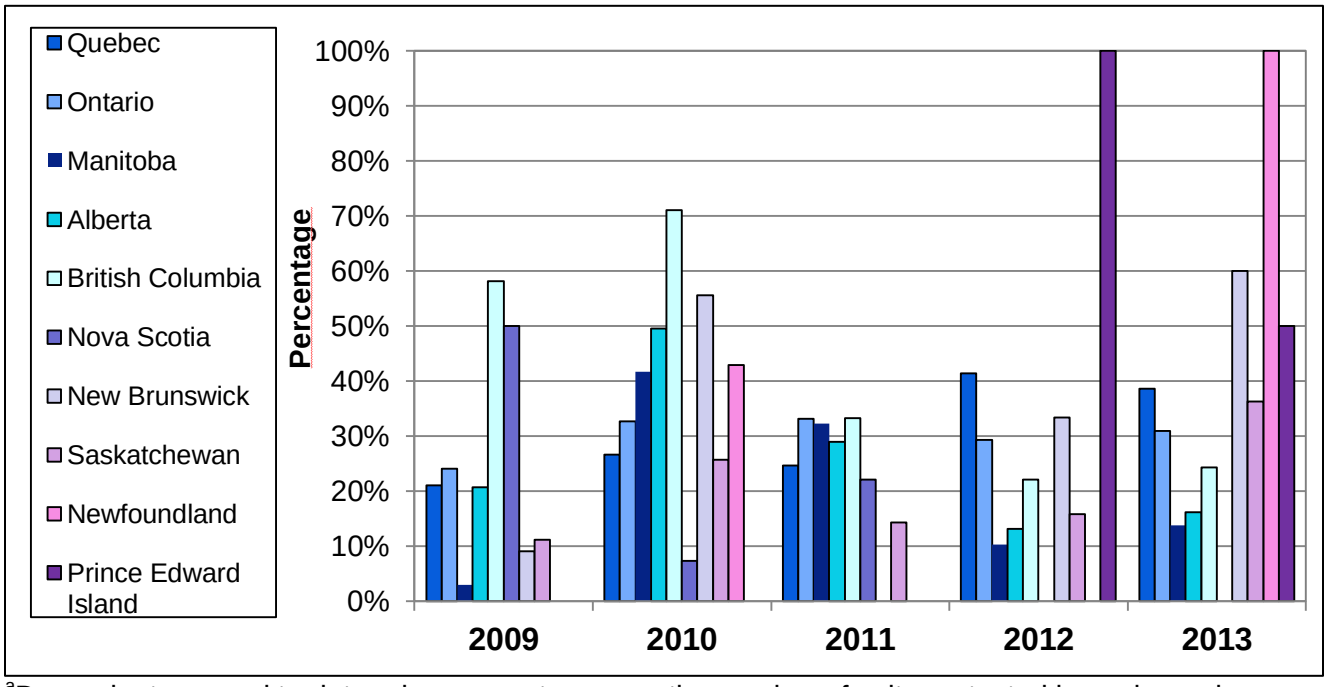
Year	Number of AziR Isolates	Percent AziR[a]	Number of AziR Isolates with CeDS and/or CxDS	Percent AziR Isolates with CeDS and/or CxDS	NG-MAST of AziR with CeDS and/or CxDS	Provinces
2012	26	0.9%	7	0.2%	ST-3158 (6); ST-1407 (1)	BC (1), ON (6)
2013	37	1.2%	8	0.3%	ST-3158 (6); ST-1407 (1); ST-9427 (1)	BC (2), SK (1), ON (5)

[a]Percentage based on the number of isolates tested nationally: 2012=3,036; 2013=3,195

CIPROFLOXACIN

The percentage of ciprofloxacin resistant isolates increased from 1.3% (59/4,458) in 2000 to 29.3% (937/3,195) in 2013. Percentage rates for each province are represented in Figure 14 and Table 13. The modal MIC of ciprofloxacin has shifted dramatically from 0.004 mg/L in 2004 to 16.0 mg/L in 2013 (Figure 15). Of the 937 ciprofloxacin resistant isolates identified in 2013, 94.6% (n=886) were also resistant to at least one other antibiotic; 41.7% (388/937) were characterized as CMRNG.

Figure 14. Geographical Distribution of Ciprofloxacin Resistant *Neisseria gonorrhoeae* Isolates, 2009 to 2013[a]



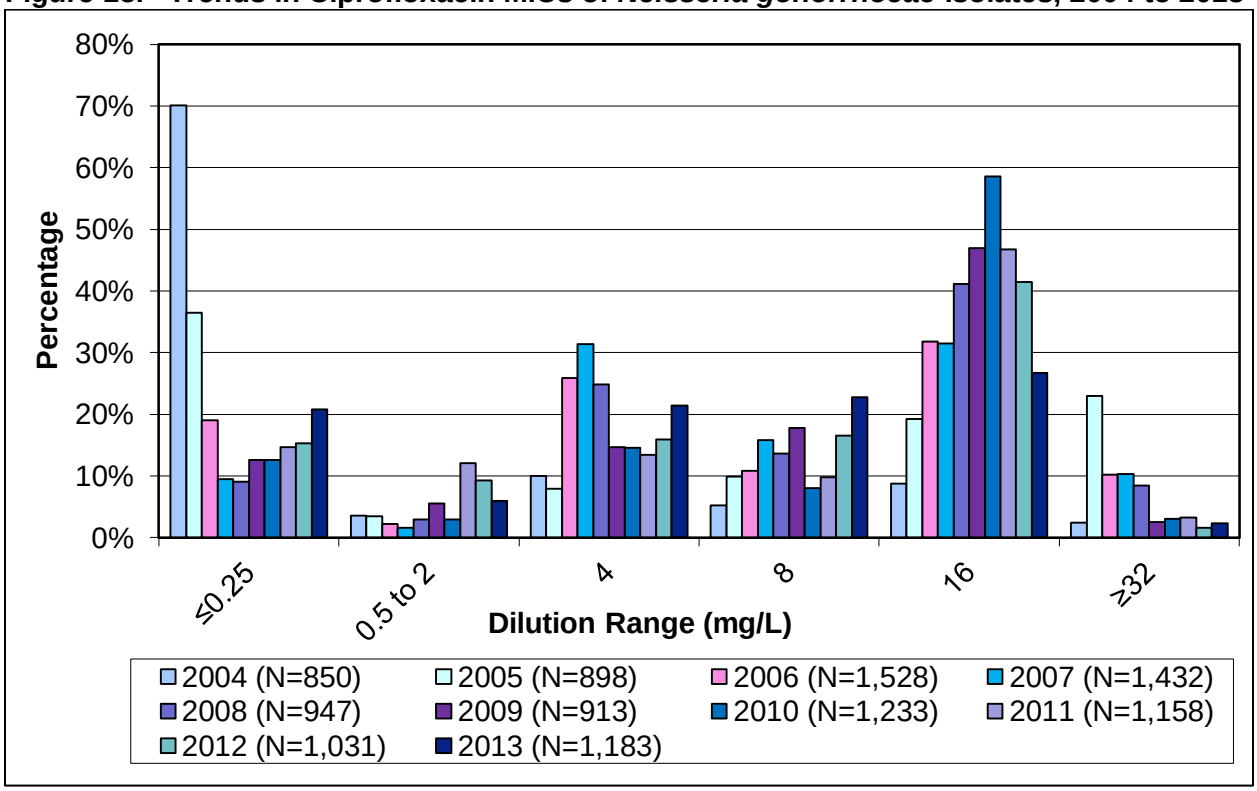
[a]Denominators used to determine percentages are the number of cultures tested in each province listed in Appendix A.

Table 13. Geographical Distribution of Ciprofloxacin Resistant *Neisseria gonorrhoeae* Isolates, 2009 to 2013[a]

Province	Year				
	2009	2010	2011	2012	2013
Quebec	202	293	257	347	276
Ontario	333	360	401	356	434
Manitoba	1	10	10	5	4
Alberta	79	140	132	65	83
British Columbia	172	243	163	82	110
Nova Scotia	1	5	17	0	0
New Brunswick	1	5	0	1	3
Saskatchewan	4	9	5	9	25
Newfoundland	0	3	0	0	1
Prince Edward Island	0	0	0	1	1
Total No. of CipR isolates	**793**	**1068**	**985**	**866**	**937**
%CipR of all isolates tested nationally	**25.5%**	**36.0%**	**29.3%**	**28.5%**	**29.3%**

[a]Percentage based on total number of isolates tested nationally: 2009=3,106; 2010=2,970; 2011=3,360; 2012=3,036; 2013=3,195

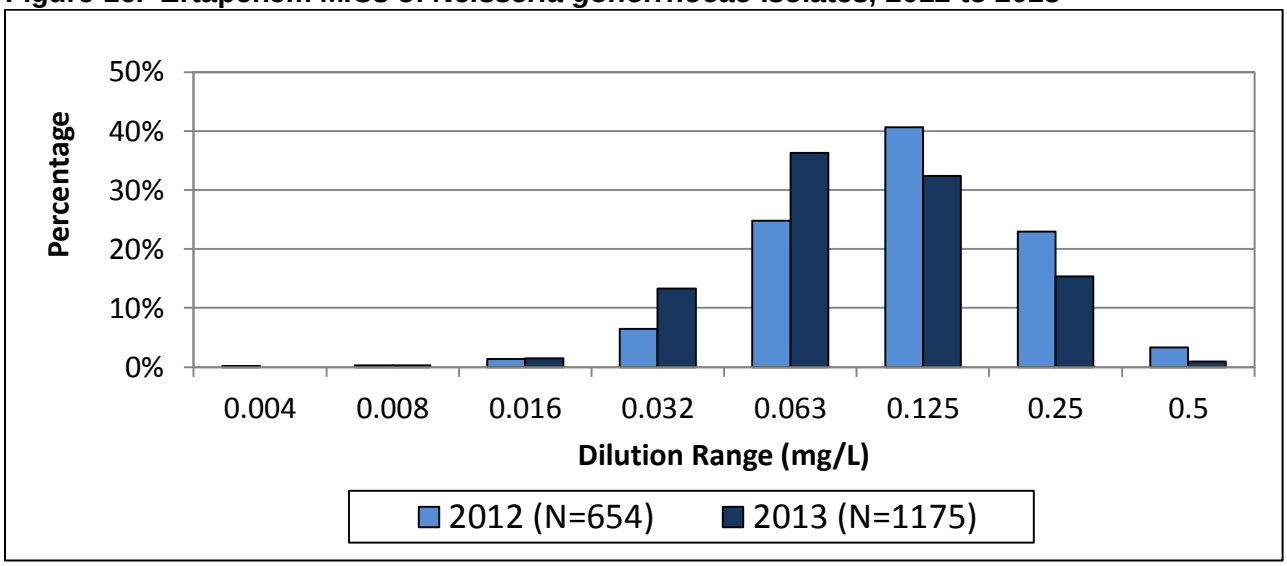
Figure 15. Trends in Ciprofloxacin MICs of *Neisseria gonorrhoeae* Isolates, 2004 to 2013



ERTAPENEM & GENTAMICIN

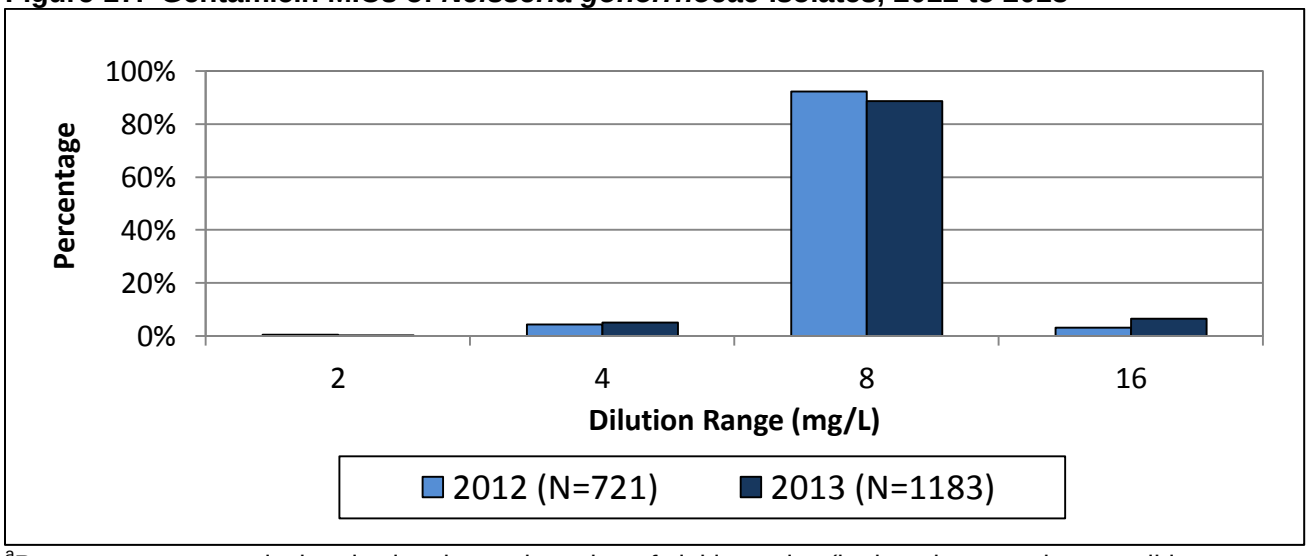
The NML began testing ertapenem and gentamicin in 2012. As there are no MIC interpretive standards for *N. gonorrhoeae* to these 2 antibiotics, only their MIC distribution is presented here. The modal MIC for ertapenem for 2013 was 0.125 mg/L which is 1 $\log_2$ dilution higher than the 2012 modal MIC (Figure 16). However, only 654 out of the 1,031 isolates of 2012 (63.4%) were tested with ertapenem. The gentamicin modal MIC for both 2012 and 2013 is 8 mg/L. There is very little variation in the gentamicin MICs (Figure 17).

Figure 16. Ertapenem MICs of *Neisseria gonorrhoeae* Isolates, 2012 to 2013 [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]ertapenem agar dilution testing started part way through 2012

Figure 17. Gentamicin MICs of *Neisseria gonorrhoeae* Isolates, 2012 to 2013[ab]



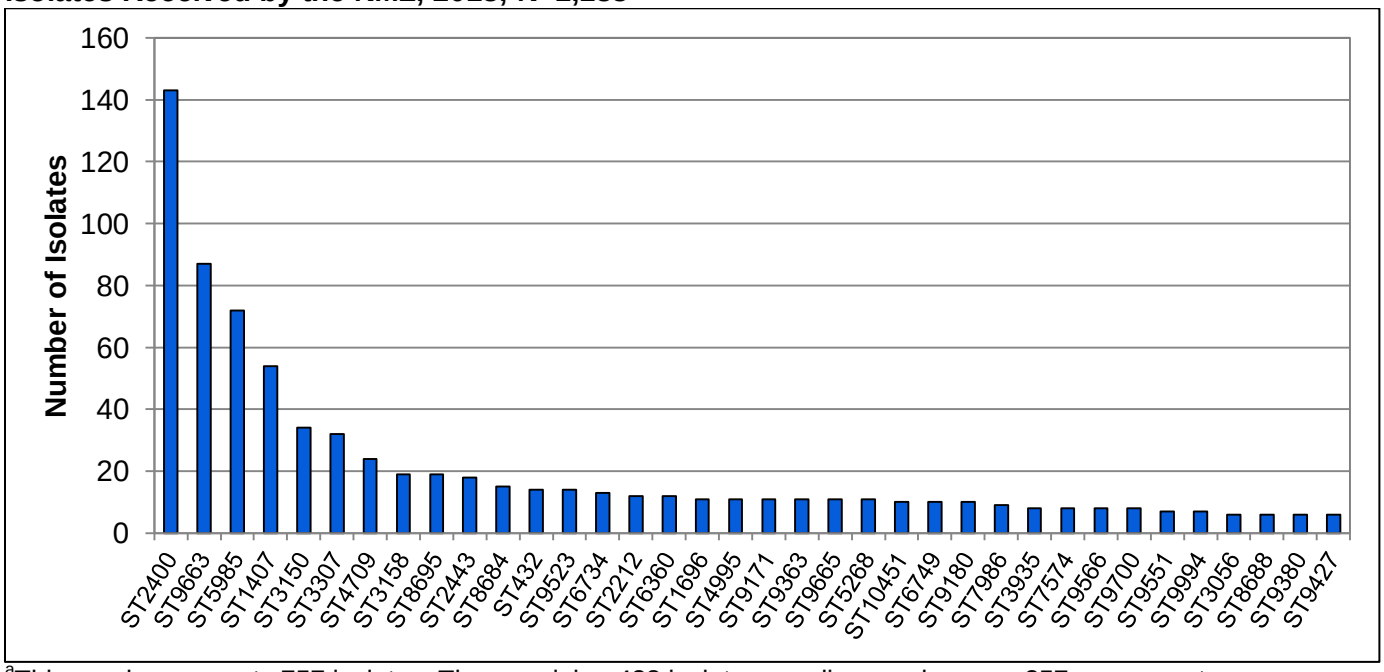
[a]Percentages were calculated using the total number of viable strains (both resistant and susceptible isolates) tested by NML as the denominator (N).
[b]gentamicin agar dilution testing started part way through 2012

NG-MAST

NG-MAST molecular-based sequence typing provides a substantial level of discrimination between isolates. In 2013, the most common sequence types (STs) identified by the NML were ST-2400 [12.1% (143/1,183)], ST-9663 [7.4% (87/1,183)] and ST-5985 [6.1% (72/1,183)], (Figure 18). Canadian isolates identified in 2013 that are highly related to ST-2400 include ST-6360 (n=12), ST-9281 (n=5) and ST-9514 (n=3) plus 14 other STs with 1 or 2 isolates in each for a total of 181 or 15.3% of isolates in the ST-2400 genogroup (STs with *tbp*B-563 and *por* alleles within 2 nucleotide base pairs of the *por* allele of ST-2400).

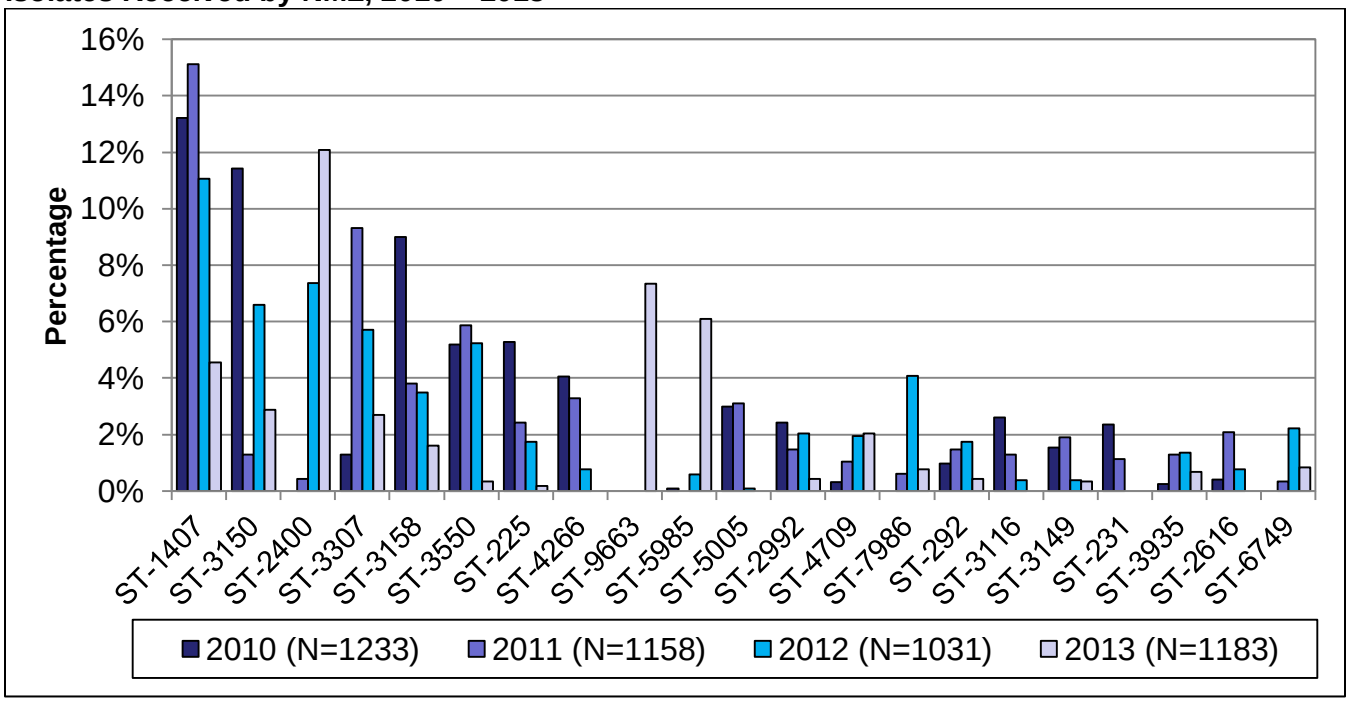
ST-2400 and ST-5985 were seen in previous years in Canada in lower numbers, however ST-9663 is a novel sequence type (Figure 19).

Figure 18. Prevalent NG-MAST Sequence Type Distribution of *Neisseria gonorrhoeae* Isolates Received by the NML, 2013; N=1,183[a]



[a]This graph represents 757 isolates. The remaining 428 isolates are dispersed among 257 sequence types (STs) containing 1 to 5 isolates each.

Figure 19. Trends of Prevalent NG-MAST Sequence Types of *Neisseria gonorrhoeae* Isolates Received by NML, 2010 – 2013[a]

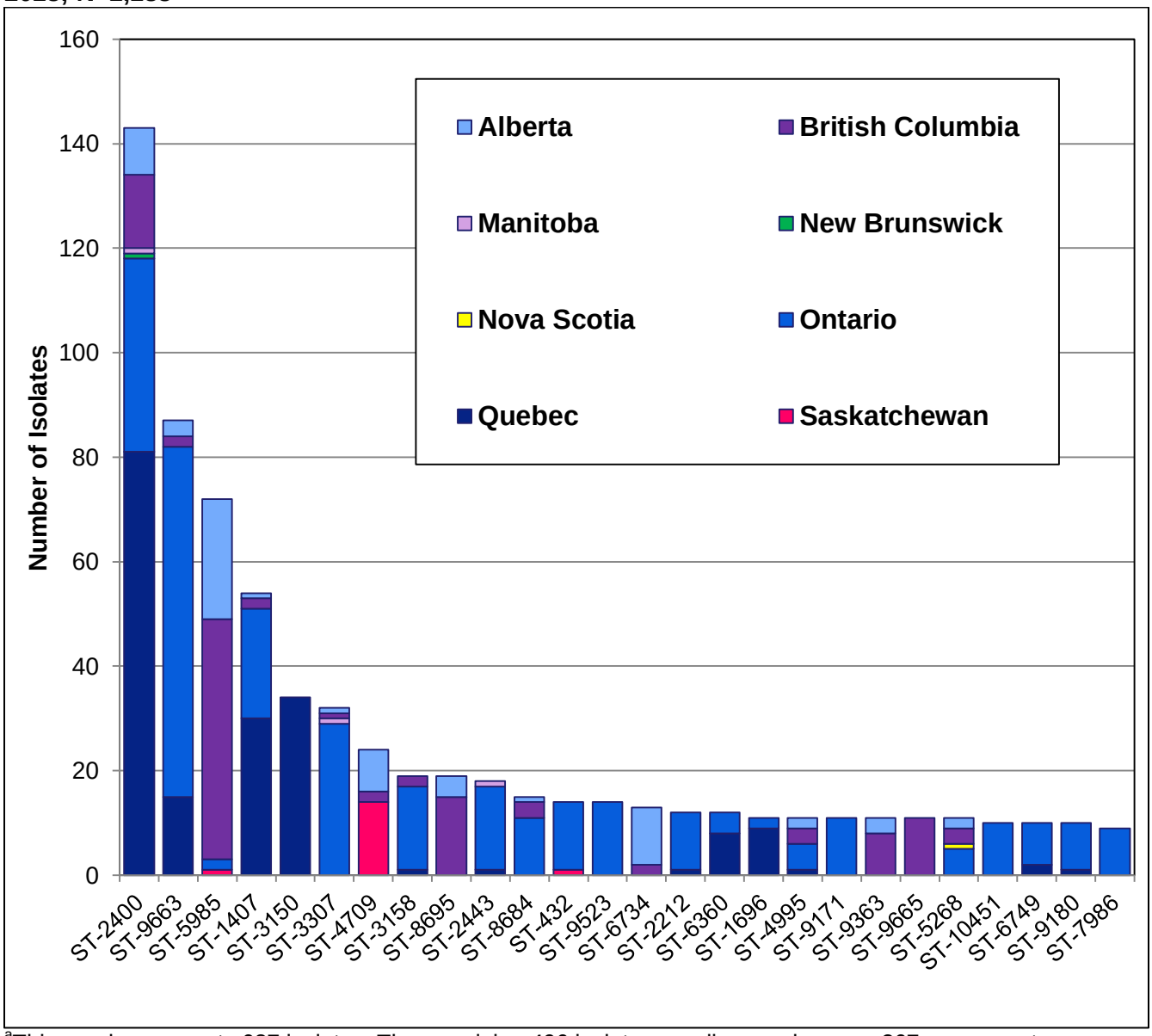


[a]A total of 249 sequence types were identified in both 2010 and 2011, 260 sequence types in 2012 and 293 sequence types in 2013. In 2010, an additional 454 isolates were identified within 230 STs. In 2011, an additional 491 isolates were identified within 229 STs; in 2012, an additional 441 isolates in 240 STs; in 2013, an additional 671 isolates in 277 STs.

ST-1407 is an internationally identified clone that has been described as a superbug, harboring high-level resistance to cephalosporins and is threatening the last recommended first-line therapy options for gonorrhoea treatment (Allen, 2013; Unemo, 2010; Unemo, 2011; Unemo, 2012). ST-1407 was the prevalent ST in 2010, 2011 and 2012. In 2013, only 4.6% (54/1,183) of isolates were identified as ST-1407. Canadian isolates identified in 2013 that are highly related to ST-1407 include ST-3158 (n=19), ST-2212 (n=12), ST-10451 (n=10), ST-9427 (n=6), plus 14 other STs with 1 to 4 isolates each. These highly related isolates are all characterized with the *tbp*B-110 allele and have *por* alleles that differ by up to 4 nucleotide base pairs. A total of 11.2% of isolates (132/1,183) were either ST-1407 or highly related sub-types of ST-1407. This percentage has decreased since 2012 which had 23.6% (243/1,031) of isolates within the ST-1407 genogroup.

Distribution of STs within provinces is represented in Figures 20 and 21. ST-2400 was identified in 6 provinces including QC [56.6% (81/143)], ON [25.9% (37/143)], BC [9.8% (14/143)], AB [6.3% (9/143)], MB [0.7% (1/143)] and NB [0.7% (1/143)]. ST-9663, the next most prevalent ST type, was identified primarily in ON [77.0% (67/87)], then QC [17.2% (15/87)], AB [3.5% (3/87)] and BC [2.3% (2/87)]. ST-5985 was identified primarily in BC [63.9% (46/72)], then AB [31.9% (23/72)], ON [2.8% (2/72)] and SK [1.4% (1/72)].

Figure 20. Provincial Distribution within *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2013; N=1,183[a]



[a]This graph represents 687 isolates. The remaining 496 isolates are dispersed among 267 sequence types (STs) containing 1 to 8 isolates each.

Figure 21. Distribution of *Neisseria gonorrhoeae* NG-MAST Sequence Types within Provinces, 2013; N=1,183[a]

[a]Manitoba (N=7): ST-2400 (n=1), ST-3307 (n=1), ST-2443 (n=1), ST-2992 (n=1), ST-6154 (n=1), ST-340 (n=1), ST-5 (n=1)
New Brunswick (N=5): ST-2400 (n=1), ST-3935 (n=1), ST-1739 (n=1), ST-5656 (n=1), ST-9727 (n=1)
Newfoundland (N=1): ST-7787 (n=1)
Nova Scotia (N=1): ST-5268 (n=1)
Prince Edward Island (N=2): ST-1117 (n=1), ST-7761 (n=1)

Figure 21a. Distribution of NG-MAST within Alberta (N=137)

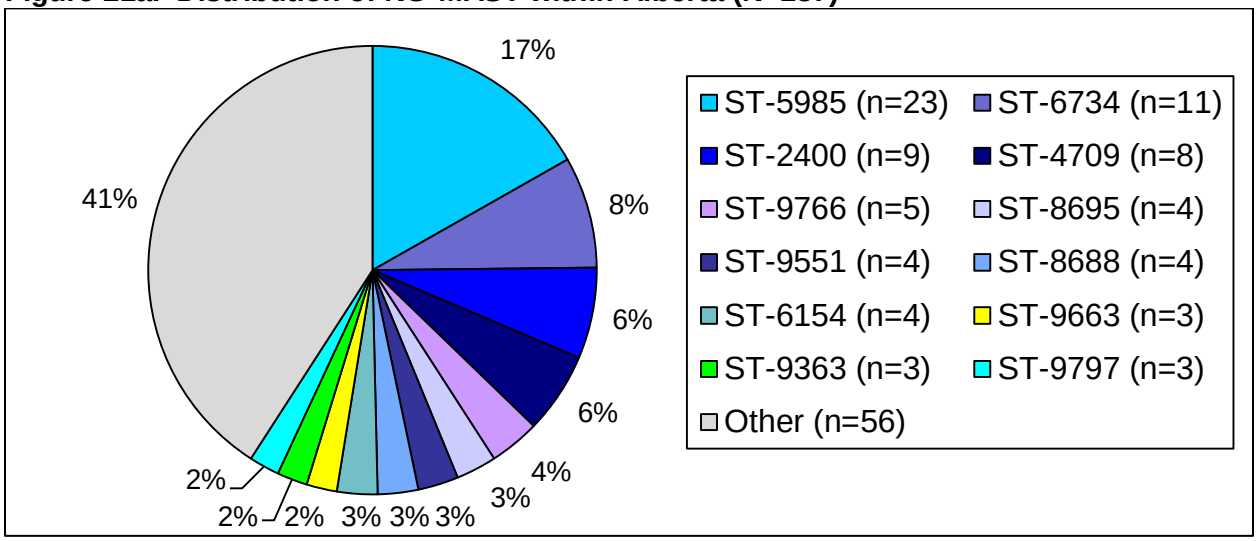


Figure 21b. Distribution of NG-MAST within British Columbia (N=170)

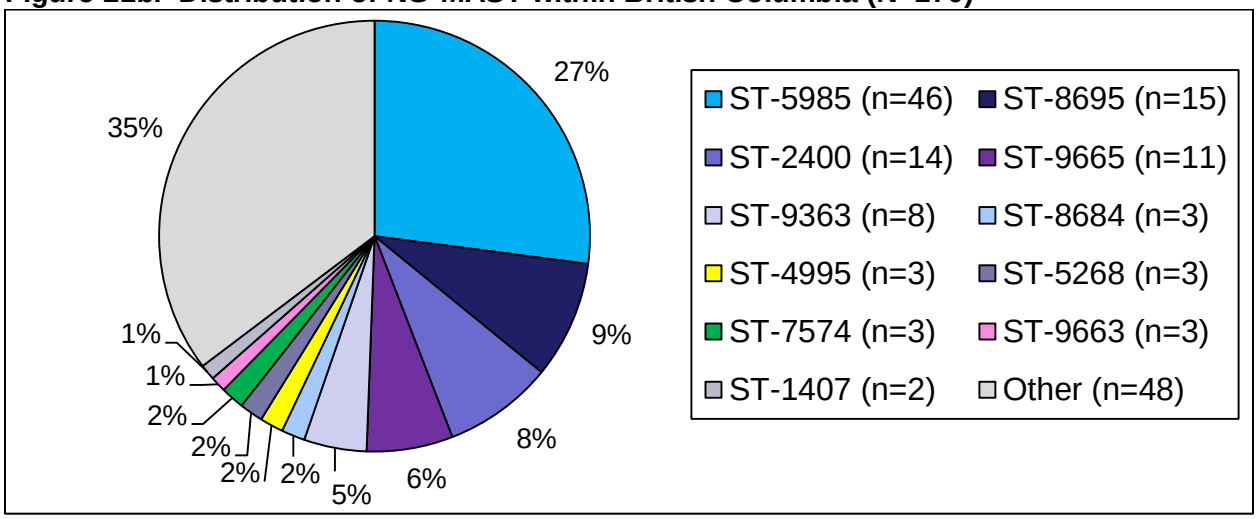


Figure 21c. Distribution of NG-MAST within Saskatchewan (N=67)

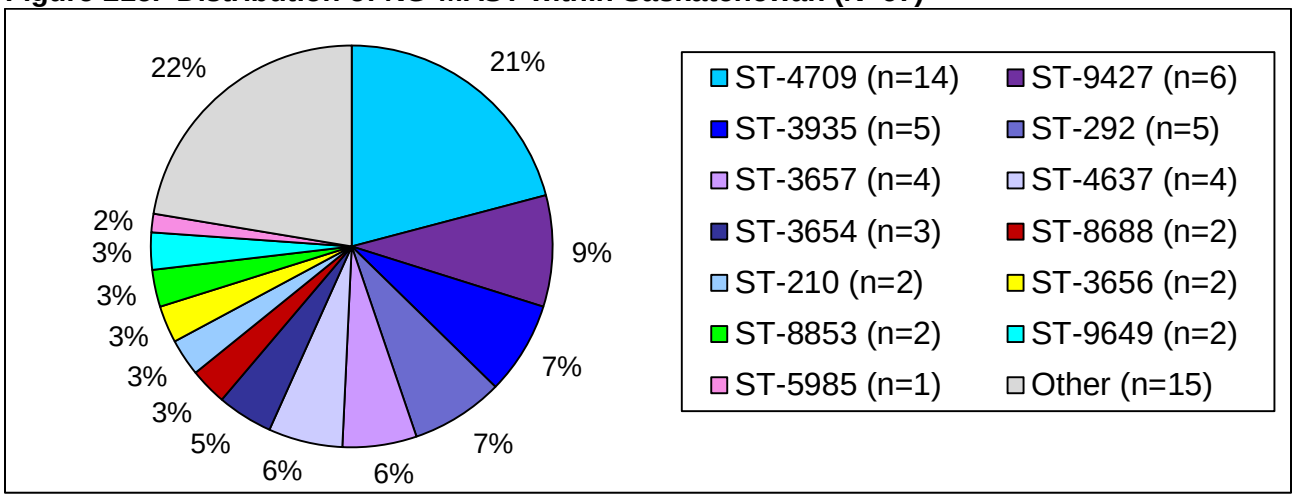


Figure 21d. Distribution of NG-MAST within Ontario (N=498)

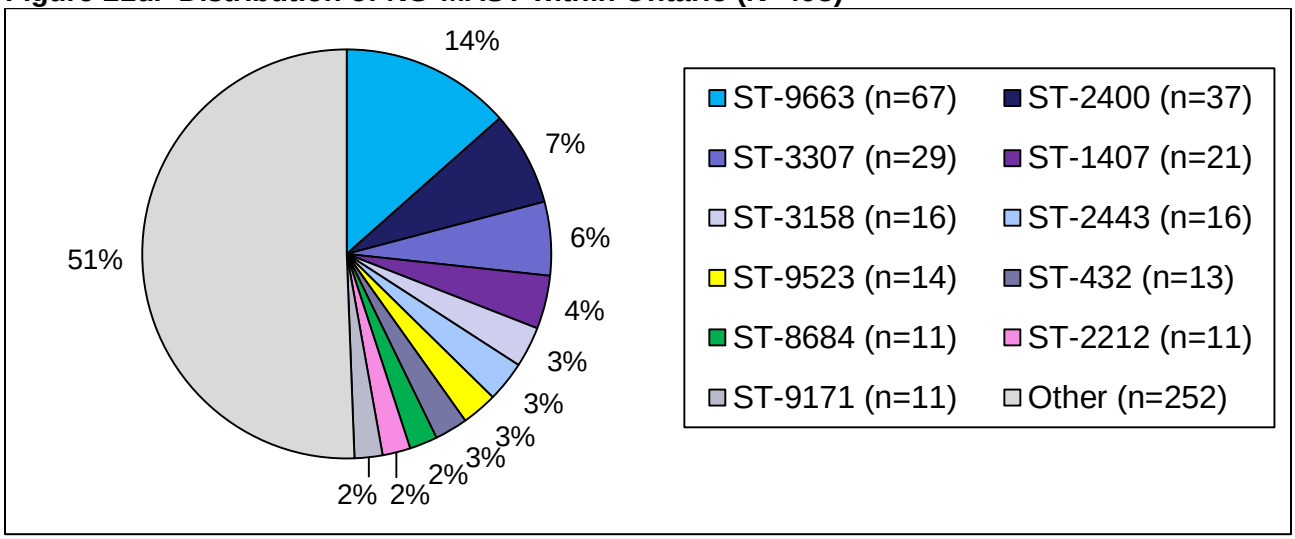


Figure 21e. Distribution of NG-MAST within Quebec (N=302)

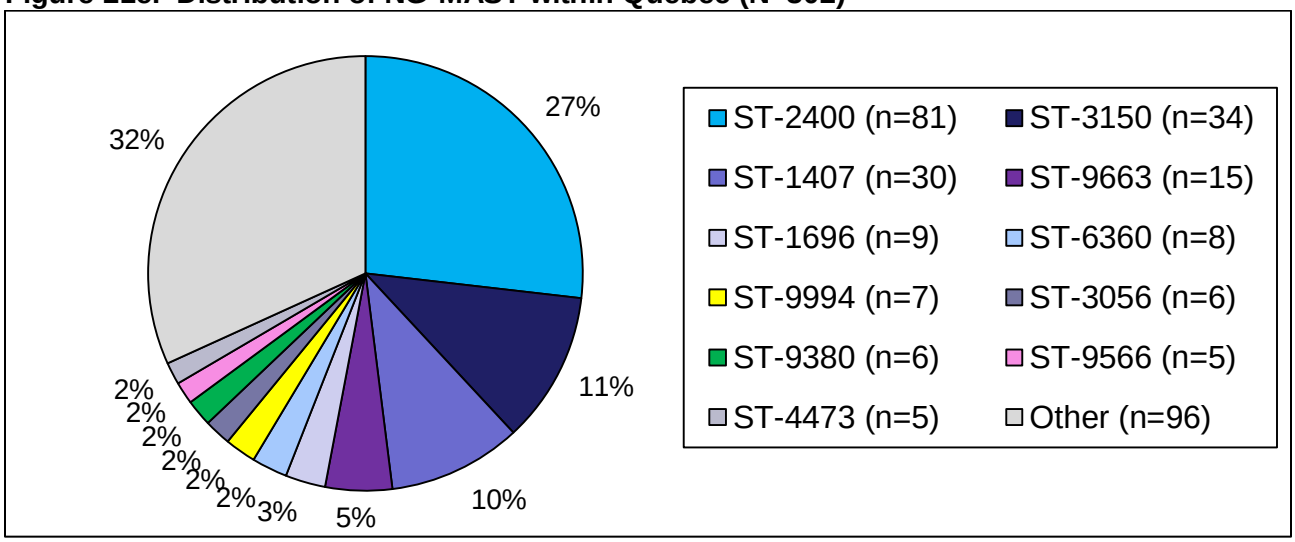
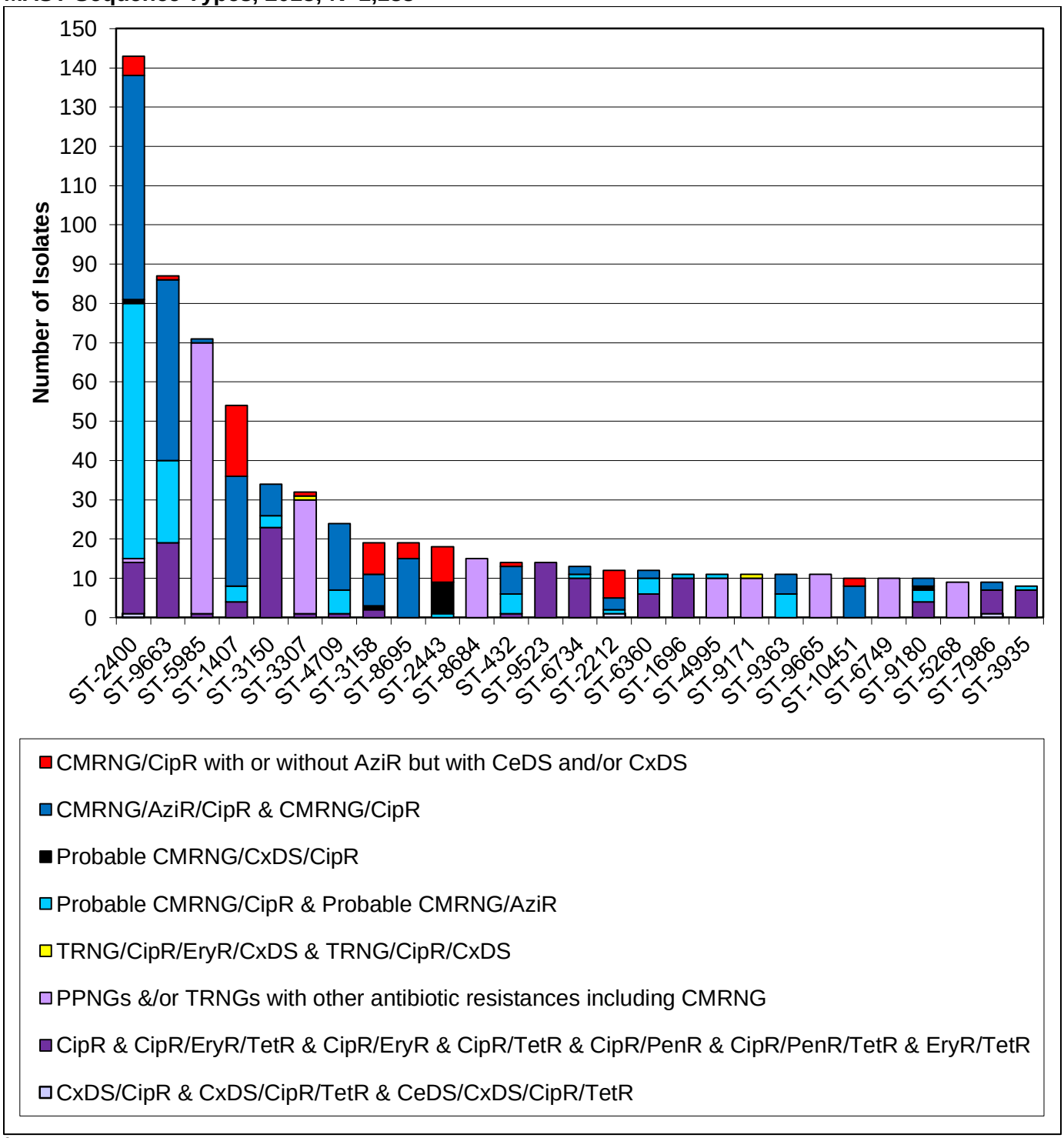


Figure 22 provides a distribution of resistance characterizations among specific ST types. ST-2400 and ST-9663 are predominantly comprised of multi-drug resistant profiles including CMRNG/Probable CMRNG along with CipR and/or CeDS and/or CxDS.

Figure 22. Distribution of Resistance Characterizations within *Neisseria gonorrhoeae* NG-MAST Sequence Types, 2013; N=1,183[a]



[a]This graph represents 692 isolates. The remaining 491 isolates are dispersed among 267 sequence types (STs) containing 1 to 8 isolates each.

Figure 23 outlines the NG-MAST sequence types of isolates with decreased susceptibility to cefixime (Figure 23a), decreased susceptibility to ceftriaxone (Figure 23b), azithromycin resistant isolates (Figure 23c) and susceptible isolates (Figure 23d).

The most prevalent ST of isolates with decreased susceptibility to cefixime was ST-1407 [23.21% (13/56)] followed by ST-9551 [12.5% (7/56)] and ST-3158 [10.7% (6/56)] (Figure 23a).

Isolates with decreased susceptibility to ceftriaxone were primarily ST-2443 [15.2% (17/112)] and ST-1407 [14.3% (16/112)] with ST-2212 and ST-3158 [7.1% (8/112)] following (Figure 23b).
The ST types identified among the AziR isolates are displayed in Figure 23c. ST-3158 [27.0% (10/37)] and ST-9427 [16.2% (6/37)] are the most prevalent. The STs of the susceptible isolates available for testing were distributed somewhat uniformly with ST-292 and ST-3657 each with 13.3% (4/30), (Figure 23d).

Figure 23. NG-MAST Sequence Types of 2013 *Neisseria gonorrhoeae* Isolates[a]

Figure 23a. Decreased Susceptibility to Cefixime (MIC ≥ 0.25 mg/L), N=56

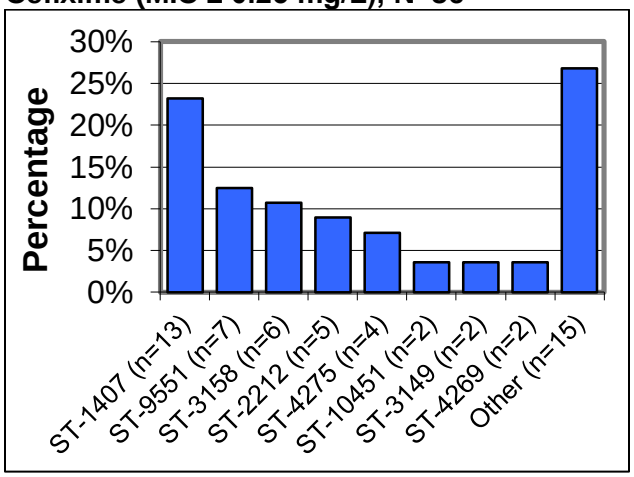


Figure 23b. Decreased Susceptibility to Ceftriaxone (MIC ≥ 0.125 mg/L), N=112

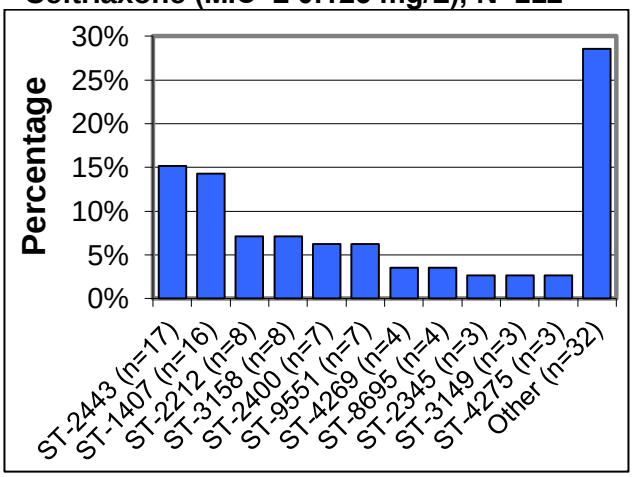


Figure 23c. Azithromycin Resistant (MIC ≥ 2 mg/L), N=37

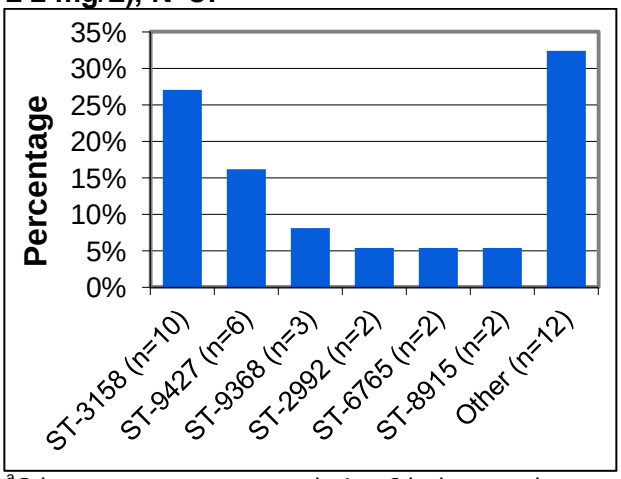
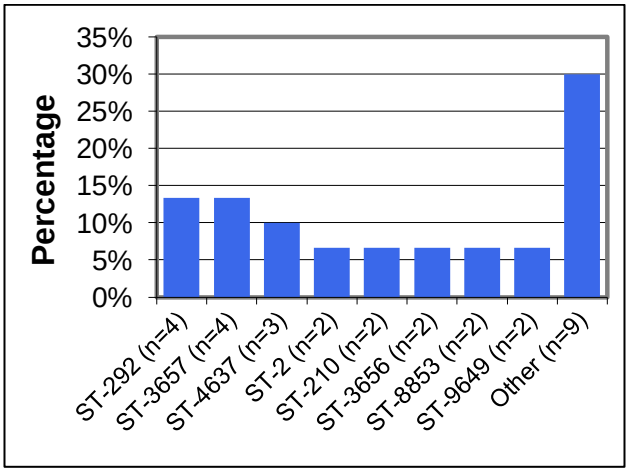


Figure 23d. Susceptible Isolates, N=30



[a]Other sequence types contain 1 or 2 isolates each

PLASMIDS

Plasmid profiles for PPNG, TRNG and PPNG/TRNG isolates are shown in Figure 24. The beta-lactamase gene was encoded in three different types of plasmids of sizes 3.05 megadaltons (Mda), 3.2 Mda and 4.5 Mda. In 2013, the 3.2 Mda plasmid was the most common type amongst the 36 PPNG strains isolated at 69.4% (25/36), followed by the 3.05 Mda plasmid at 27.8% (10/36) and then the 4.5 Mda plasmid at 2.8% (1/36). These plasmids co-existed with the 2.6 Mda cryptic plasmid and sometimes with the 24.5 Mda conjugal plasmid. The 3.2 Mda plasmid is also the most common β-lactamase encoding plasmid in PPNG/TRNG strains at 74.0% (74/100). The 25.2 Mda plasmid that encodes tetracycline resistance (TetM) co-existed with the cryptic plasmids in most TRNG and PPNG/TRNG strains. Among the TRNG isolates tested in 2013, 61.9% (112/181) had the 2.6 and 25.2 Mda plasmids. TRNG isolates accounted for 88.6% of all the plasmid mediated resistance in *N. gonorrhoeae* in 2013 (281/317 PPNG, PPNG/TRNG and TRNG strains).

Figure 24. Plasmid Distribution within Antimicrobial Classifications of *Neisseria gonorrhoeae* Isolates Received by the NML, 2013

Figure 24a. PPNG (N=36)

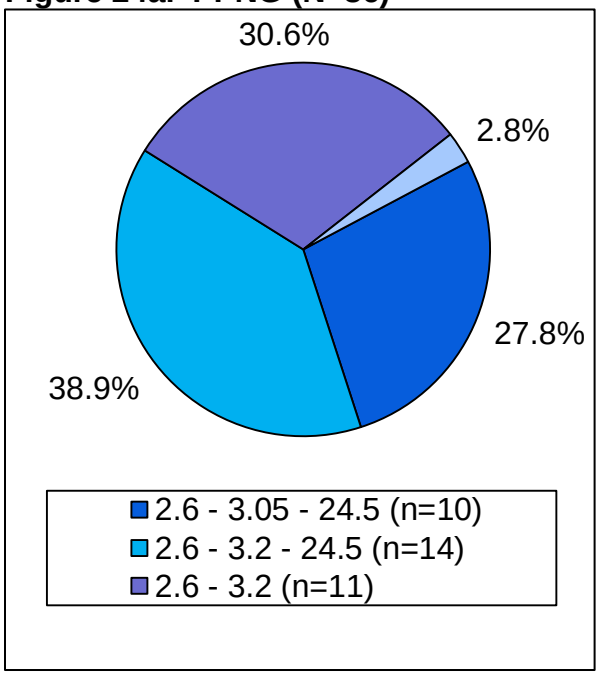


Figure 24b. PPNG/TRNG (N=100)

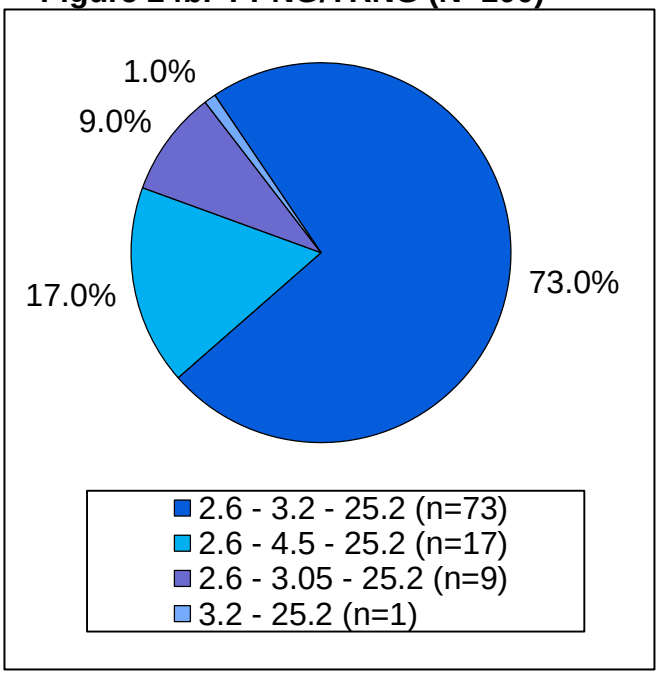
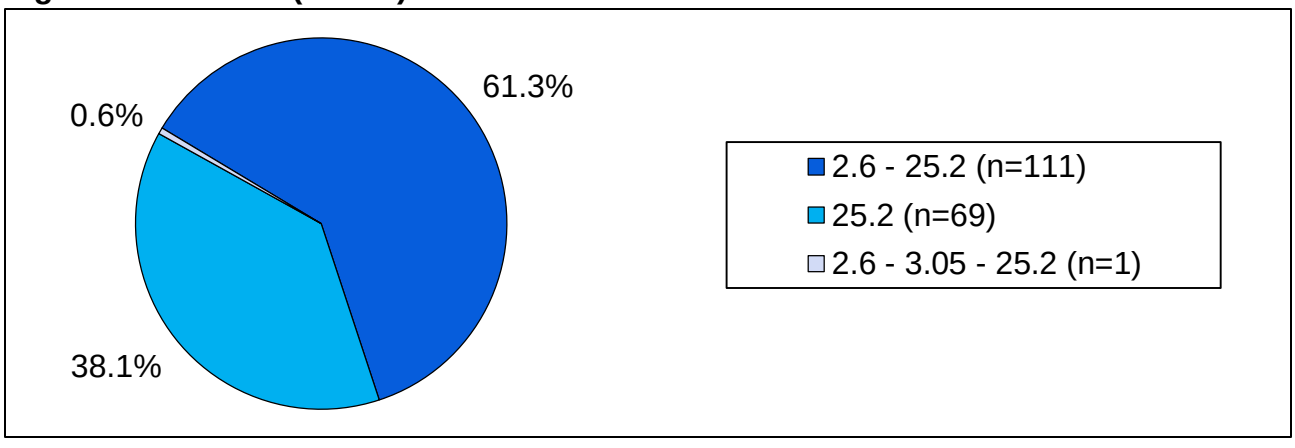


Figure 24c. TRNG (N=181)



CONCLUSION

The evolution of antimicrobial resistance in gonorrhoea is complex and 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 gonorrhoea. 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. 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 gonorrhoea treatment changes. In 2011, The Canadian STI Guidelines issued updated recommendations for the use of combination gonorrhoea 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 gonorrhoea treatment recommendations in Canada there has been a decrease in the proportion of isolates with elevated MICs to the cephalosporins. In 2011, 7.6% of isolates exhibited decreased susceptibility to ceftriaxone and/or cefixime according to the WHO definition (decreased susceptibility MICs ≥0. 25 mg/L for cefixime and ≥0.125 mg/L for ceftriaxone). This decreased to 5.9% in 2012 and further declined to 3.9% of isolates tested in 2013. Similarly, the US reported declines to decreased cefixime susceptibility from 3.9% in 2010 to 2.9% in the first half of 2012 (Kirkcaldy, 2013). The UK reported the prevalence of isolates with decreased cefixime susceptibility dropped from 17.1% in 2010 to 10.8% in 2011 (Ison, 2013).

Enhancing surveillance to include linked epidemiological and laboratory data will assist with the limitations in the current passive surveillance system regarding data representativeness and interpretation. These improvements to the gonococcal surveillance program are expected with the ESAG (Enhanced Surveillance of Antimicrobial Resistant Gonorrhoea) program beginning in 2014.

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 gonorrhoea. This surveillance is particularly important as molecular testing, which provides no susceptibility data becomes the most commonly used method for the diagnosis of *N. gonorrhoeae* in Canada.

APPENDIX A

Neisseria gonorrhoeae culture isolates in Canada, 2009 – 2013[a]

Province	2009 GC Cultures			2010 GC Cultures			2011 GC Cultures			2012 GC Cultures			2013 GC Cultures		
	Tested in each province	Received at NML	% Sent to NML for Testing	Tested in each province	Received at NML	% Sent to NML for Testing	Tested in each province	Received at NML	% Sent to NML for Testing	Tested in each province	Received at NML	% Sent to NML for Testing	Tested in each province	Received at NML	% Sent to NML for Testing
British Columbia	296	183	61.80%	342	256	74.90%	490	176	35.90%	372	92	24.70%	454	170	37.40%
Alberta	383	91	23.50%	283	164	58.00%	457	156	34.10%	497	94	18.90%	514	134	26.10%
Saskatchewan	36	30	83.30%	35	11	31.40%	35	35	100%	57	57	100%	69	67	97.10%
Manitoba	34	3	8.80%	24	11	45.80%	31	12	38.70%	49	8	16.30%	29	7	24.10%
Ontario	1,383	383	27.70%	1,101	383	34.80%	1,212	428	35.30%	1,218	403	33.10%	1,404	498	35.50%
Québec	959	216	22.50%	1,100	335	30.50%	1,045	282	27.00%	838	390	46.50%	716	298	41.60%
New Brunswick	11	4	36.40%	9	9	100%	12	6	50.00%	3	3	100%	5	5	100%
Nova Scotia	103	2	1.90%	69	69	100%	77	77	100%	0	0	n/a	1	1	100%
Newfoundland	2	2	100%	7	7	100%	1	0	0%	1	0	0%	1	1	100%
Prince Edward Island	0	0	n/a	0	0	n/a	0	0	n/a	1	1	100%	2	2	100%
Totals	**3,207**	**914**	**28.50%**	**2,970**	**1,245**	**41.90%**	**3,360**	**1,172**	**34.90%**	**3,036**	**1,048**	**34.50%**	**3,195**	**1,183**	**37.00%**

[a]No Neisseria gonorrhoeae cultures were reported to the NML or received from the Northwest Territories, Nunavut or the Yukon in 2009 to 2013

APPENDIX B

Characterization of all *Neisseria gonorrhoeae* Isolates Submitted to the NML, 2009 - 2013

Characterization		2009	2010	2011	2012	2013	Totals
Plasmid Mediated Resistances	PPNG	8	7	2	3	3	**23**
	PPNG/CipR	11	10	9	6	10	**46**
	PPNG/EryR	2	1	6	1	11	**21**
	PPNG/EryR/CipR	0	1	0	2	0	**3**
	PPNG/TetR	3	1	0	2	0	**6**
	PPNG/TetR/CipR	2	1	1	4	4	**12**
	PPNG/CMRNG	0	0	2	2	4	**8**
	PPNG/CMRNG/CipR	3	3	6	10	4	**26**
	PPNG/CMRNG/CxDS/CipR	0	0	1	0	0	**1**
	PPNG/TRNG	11	0	2	11	18	**42**
	PPNG/TRNG/CeDS/CipR	0	0	2	0	0	**2**
	PPNG/TRNG/CeDS/CipR/EryR	0	0	6	0	0	**6**
	PPNG/TRNG/CeDS/CxDS/CipR/EryR	0	0	3	0	0	**3**
	PPNG/TRNG/CipR	33	32	43	49	43	**200**
	PPNG/TRNG/EryR	1	0	0	0	3	**4**
	PPNG/TRNG/CipR/EryR	4	7	34	22	34	**101**
	PPNG/TRNG/CxDS/CipR/EryR	0	2	14	0	0	**16**
	PPNG/TRNG/AziR/CipR/EryR	1	0	0	0	1	**2**
	PPNG/TRNG/AziR/CipR/CxDS/EryR	1	1	0	0	0	**2**
	TRNG	28	12	21	36	86	**183**
	TRNG/CipR	12	22	15	16	29	**94**
	TRNG/CipR/CxDS	0	0	0	0	1	**1**
	TRNG/CipR/EryR	4	11	36	47	42	**140**
	TRNG/CipR/EryR/CeDS	0	0	1	0	0	**1**
	TRNG/CipR/EryR/CeDS/CxDS	0	0	1	0	0	**1**
	TRNG/CipR/EryR/CxDS	0	0	8	0	1	**9**
	TRNG/CxDS	0	0	0	1	0	**1**
	TRNG/EryR	5	6	1	1	13	**26**
	TRNG/CipR/PenR	0	0	1	0	2	**3**
	TRNG/CxDS/CipR	0	0	1	1	1	**3**
	TRNG/CMRNG	0	0	0	1	2	**3**
	TRNG/CMRNG/CipR	2	1	2	2	4	**11**
	TRNG/CMRNG/CxDS/CipR	0	1	2	3	0	**6**
	TRNG/PenR	0	0	1	1	1	**3**
	Total	**131**	**119**	**221**	**221**	**317**	**1,009**

Characterization		2009	2010	2011	2012	2013	Totals
Chromosomal Mediated Resistances	AziR/EryR	0	21	5	0	3	**29**
	AziR/EryR/TetR	1	2	2	14	8	**27**
	AziR/CipR/EryR	0	0	0	0	1	**1**
	AziR/EryR/PenR	0	0	1	0	0	**1**
	AziR/CipR/EryR/TetR	0	0	0	0	2	**2**
	AziR/CeDS/CipR/EryR/TetR	0	0	0	0	1	**1**
	CeDS/CipR/EryR	0	1	0	0	0	**1**
	CeDS/CipR/TetR	0	0	0	1	0	**1**
	CeDS/CxDS/CipR	0	0	0	0	1	**1**
	CeDS/CxDS/CipR/PenR	0	0	0	0	2	**2**
	CeDS/CxDS/CipR/TetR	0	0	0	0	3	**3**
	CeDS/CxDS/CipR/PenR/TetR	0	0	0	0	1	**1**
	CeDS/CipR/PenR/TetR	0	0	1	0	0	**1**
	CxDS/CipR/EryR/TetR	0	0	1	1	0	**2**
	CipR	40	54	34	44	51	**223**
	CipR/CeDS	0	0	0	0	1	**1**
	CipR/CxDS	0	1	0	0	2	**3**
	CipR/EryR	37	10	16	3	2	**68**
	CipR/EryR/TetR	8	15	9	4	34	**70**
	CipR/PenR	0	0	0	0	2	**2**
	CipR/PenR/TetR	0	0	0	2	2	**4**
	CipR/TetR	26	26	23	56	70	**201**
	CipR/TetR/CxDS	0	1	0	3	2	**6**
	EryR	1	0	9	3	3	**16**
	EryR/TetR	0	3	16	10	13	**42**
	PenR	1	0	0	0	1	**2**
	PenR/TetR	0	0	0	0	2	**2**
	TetR	9	9	17	21	8	**64**
	CMRNG	3	3	2	4	26	**38**
	CMRNG/AziR/CipR	8	8	5	5	7	**33**
	CMRNG/AziR/CeDS/CxDS/CipR	0	0	0	1	4	**5**
	CMRNG/AziR/CipR/CxDS	0	2	0	6	2	**10**
	CMRNG/AziR/CeDS/CipR	0	0	0	0	1	**1**
	CMRNG/CipR	367	443	387	294	295	**1,786**
	CMRNG/AziR	0	1	0	0	4	**5**
	CMRNG/CeDS/CipR	3	8	32	7	6	**56**
	CMRNG/CeDS/CxDS/CipR	32	79	88	55	30	**284**
	CMRNG/CxDS/CipR	60	104	80	92	43	**379**
	Probable CMRNG	6	4	3	9	6	**28**
	Probable CMRNG/AziR	0	0	0	0	1	**1**
	Probable CMRNG/AziR/CipR	0	2	0	0	2	**4**
	Probable CMRNG/CeDS	0	0	0	1	0	**1**
	Probable CMRNG/CipR	137	194	110	123	174	**738**
	Probable CMRNG/CeDS/CipR	0	0	5	2	1	**8**
	Probable CMRNG/CeDS/CxDS/CipR	0	10	1	1	5	**17**
	Probable CMRNG/CxDS/CipR	3	17	7	4	14	**45**
	Susceptible Strain	40	96	83	44	30	**293**
	Total	**782**	**1,114**	**937**	**810**	**866**	**4,509**

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