

Government  
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Alberta Health  
Services

2013

## Gonorrhea Antimicrobial Resistance in Alberta

Gonorrhea Antimicrobial Resistance

Alberta Gonorrhea AMR  
Surveillance Working Group  
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## Background

Gonorrhoea is the second most common notifiable sexually transmitted infection (STI) in Canada. The incidence of gonorrhoea in Canada has been increasing since 1998 and the national gonorrhoea rate was 36.2 per 100,000 in 2012.<sup>1</sup> In Alberta, the provincial rate was 49.0 per 100,000 in 2013, with rates varying widely by zone (9.8/100,000 in the South Zone and 108.4/100,000 in the North Zone).<sup>2</sup> Infections can result in significant morbidity and increase the risk of HIV transmission and acquisition.<sup>1</sup>

Since the 1940s, gonorrhoea has developed resistance to multiple classes of antibiotics.<sup>3</sup> Following the widespread global use of oral cephalosporins for the treatment of gonorrhoea, initial reports of gonococci with reduced susceptibility and cases of treatment failure were reported in Japan.<sup>4,5</sup> Similar cases have since been reported from other parts of the world.<sup>3</sup> The creep of minimum inhibitory concentration (MIC) to expanded spectrum cephalosporins (ESC) continues to be reported in Canada and around the world.<sup>6-9</sup> The association of certain sequence types with decreased susceptibility to ESC continues to grow.<sup>10-13</sup> In addition, concerns with the use of azithromycin monotherapy have arisen as azithromycin resistance has emerged and continues to rise.<sup>9,14,15</sup>

Due to rising rates of antimicrobial resistance (AMR) to the ESCs cefixime and ceftriaxone among gonococcal isolates in Canada, national treatment guidelines were revised in December 2011 and higher doses were recommended; this recommendation was communicated to Alberta physicians in February 2012. In February 2013, updated Alberta Treatment Guidelines for STI were released emphasizing the use of dual therapy for the treatment of gonorrhoea (cefixime 800 mg plus azithromycin 1 gm for heterosexuals and pregnant women and ceftriaxone 250 mg plus azithromycin 1 gm for men who have sex with men and all pharyngeal infections).

In light of these observations, surveillance of the epidemiology of AMR in gonococcal isolates collected through Alberta's established surveillance system continues.<sup>16</sup>

## Objectives

The objectives of this analysis were:

1. To examine demographic and behavioural characteristics among culture positive gonorrhoea cases.
2. To examine the trends in AMR to multiple antibiotics on gonococcal isolates collected through Alberta's surveillance system.
3. To examine the trends in sequence typing data and its relationship to AMR.

## Methods

Under Alberta's Public Health Act, all positive gonorrhea results are reportable by all testing laboratories as well as testing clinicians to the designate of the provincial chief and senior medical officer of health (Alberta Health Services [AHS] Sexually Transmitted Infections Centralized Services). Gonorrhea is diagnosed by either nucleic acid amplification testing (NAAT) and/or culture. The Calgary and Edmonton STI clinics routinely screen using both methods. All clinical and behavioural data are submitted by the testing clinician on a STI Notifiable Disease Form and entered into a provincial database (AHS' STI module of the Communicable Disease Registry System [CDRS]). In addition, the Provincial Laboratory for Public Health (ProvLab) routinely conducts E-tests for susceptibility to multiple antibiotics on culture-based specimens and reports to the testing clinician the results of susceptibility testing on antibiotics currently recommended for treatment in the Alberta Treatment Guidelines for STI.<sup>17</sup> Isolates demonstrating resistance and isolates with cefixime MIC values of  $\geq 0.06$   $\mu\text{g/mL}$  (beginning in 2011) are submitted to the National Microbiology Laboratory for sequence typing.

### Data and Analysis

Data on culture positive isolates from ProvLab during 2007-2013 were extracted from the ProvLab database. If more than one culture positive specimen per patient was submitted on the same day, only one isolate was selected for data analysis. MIC data for duplicate/triplicate specimens from the same patient submitted on the same day with the same sequence typing data were reviewed, and the most resistant isolate was selected. If MIC patterns were the same for multiple isolates, the following hierarchy was used to select the isolate: throat/genital/rectum.

A data extract of gonorrhea cases during the same time period was obtained from CDRS. CDRS data was merged with the ProvLab line list by specimen number. In 2013, 602 gonorrhea isolates were identified; however, 95 specimens were excluded for various reasons (Figure 1).

Criteria for interpretation of MIC values were based on Clinical Laboratory Standards Institute (CLSI) standards (Table 1).<sup>18</sup> Breakpoints for resistance to cefixime and ceftriaxone have not been defined by CLSI. However, isolates with an MIC of  $\leq 0.25$   $\mu\text{g/mL}$  are considered susceptible. None of the isolates submitted between 2007 and 2013 had a MIC value  $> 0.25$   $\mu\text{g/mL}$  for cefixime; therefore to understand characteristics associated with rising MIC values, cefixime MIC values were grouped into 2 categories:  $\leq 0.016 - 0.03$   $\mu\text{g/mL}$  and  $0.06 - 0.25$   $\mu\text{g/mL}$ . CLSI does not provide interpretive criteria for azithromycin; an MIC value of  $\geq 2.0$   $\mu\text{g/mL}$  is considered to have decreased susceptibility by the U.S. Gonococcal Isolate Surveillance Project.<sup>19</sup>

Figure 1. Data Exclusion 2013

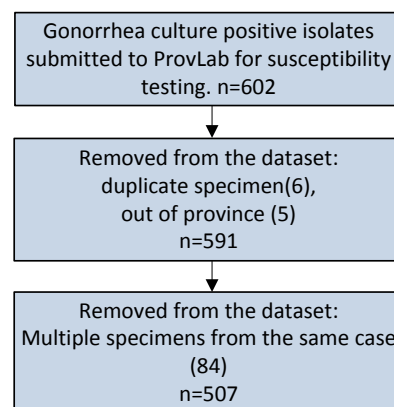


Table 1. Clinical Laboratory Standards Institute criteria for MIC Interpretations

	MIC ( $\mu\text{g/mL}$ )		
	Susceptible	Intermediate	Resistance
Penicillin	$\leq 0.06$	0.125-1.0	$\geq 2.0$
Tetracycline	$\leq 0.25$	0.5-1.0	$\geq 2.0$
Ciprofloxacin	$\leq 0.06$	0.125-0.5	$\geq 1.0$
Cefixime	$\leq 0.25$	-	-
Ceftriaxone	$\leq 0.25$	-	-

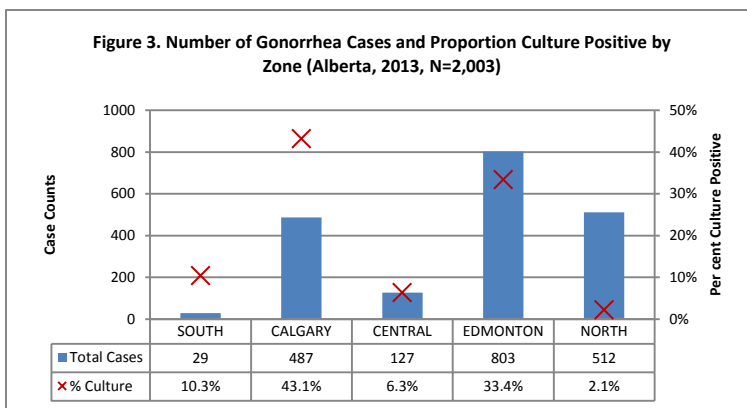
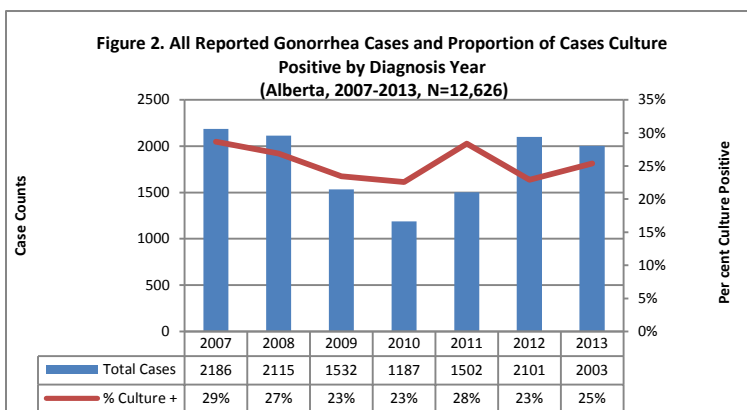
A data extract of all gonorrhea cases was provided from the STI module of CDRS to compare cases with culture results available to NAAT-only cases. An extract of 2013 treatment data was also provided. As multiple drugs may be prescribed for gonorrhea cases, all treatments were reviewed to identify the use of a preferred or alternate treatment regime according to the 2012 Alberta STI Treatment guidelines. P-values were calculated using chi-square or Fisher’s exact test depending on cell size. IBM SPSS Statistics version 19 was used to complete the analysis.

**Results**

**Sampling of Culture Positive Cases**

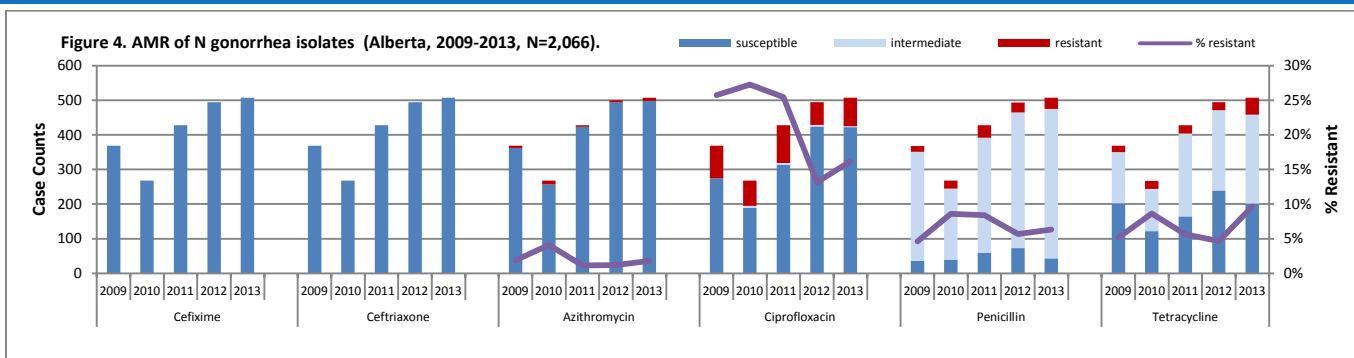
In Alberta, 2,003 cases of gonorrhea were reported in 2013. One-quarter of the cases (25.4%; n=508) were diagnosed by culture with the remainder of the cases identified through NAAT (Figure 2). While the Calgary and Edmonton zones have the highest proportion of cases tested by culture (43.1% and 33.4%, respectively), the North Zone had the lowest proportion of gonorrhea cases tested by culture (2.1%) while reporting 25.6% of provincial cases (Figure 3).

The majority (92.5%, n=470) of culture positive cases were collected from the Calgary and Edmonton STI Clinics. Cases tested by culture were more likely to be male, older, Caucasian, and report same sex partners (Table 2).



**Table 2. Characteristics of Gonorrhea Cases by Culture versus NAAT Methods (Alberta, 2013, N=2,003).**

	Test Type n(%)			p-value
	Culture (N=508)	NAAT-only (n=1,495)	Total (N-2,003)	
Male	411 (80.9)	702 (47.0)	1,113 (55.6)	<0.001
Median Age (IQR)	27 (22-33)	24 (20-30)	25 (20-30)	<0.001
<b>Ethnicity</b>				
Aboriginal	93 (18.3)	618 (41.3)	711 (35.5)	<0.001
Asian	39 (7.7)	50 (3.3)	89 (4.4)	
Black	33 (6.6)	66 (4.4)	99 (4.9)	
Caucasian	319 (62.8)	451 (30.2)	770 (38.4)	
Other	12 (2.4)	11 (0.7)	23 (1.1)	
Unknown	12 (2.4)	299 (20.0)	311 (15.5)	
<b>Reported Sexual Partners</b>				
Heterosexual	246 (48.4)	1,1082	1,348 (67.3)	<0.001
Same sex	222 (43.7)	72 (4.8)	294 (14.7)	
Bisexual	30 (5.9)	45 (3.0)	75 (3.7)	
<12 years	1 (0.2)	1 (0.1)	2 (0.1)	
Unknown	9 (1.8)	275 (18.4)	284 (14.2)	
<b>Case Zone</b>				
North	11 (2.2)	501 (33.5)	512 (25.6)	<0.001
Edmonton	268 (52.8)	535 (35.8)	803 (40.1)	
Central	8 (1.6)	119 (8.0)	127 (6.3)	
Calgary	210 (41.3)	277 (17.5)	487 (24.3)	
South	3 (0.6)	26 (1.7)	29 (1.4)	
Zone Not Identified	8 (1.6)	37 (2.5)	45 (2.2)	
<b>Testing Agency</b>				
STI Clinics	470 (92.5)	197 (13.2)	667 (33.3)	<0.001
Other Providers	38 (7.5)	1,298 (86.8)	1,336 (66.7)	



**Table 3. Cefixime, Ceftriaxone and Azithromycin MIC value Distribution by Received Year (Alberta, 2009-2013, N=2,066)**

Year	n	Cefixime (µg/mL)		Ceftriaxone (µg/mL)		Azithromycin (µg/mL)		Ciprofloxacin (µg/mL)	
		Range	MIC <sub>90</sub>	Range	MIC <sub>90</sub>	Range	MIC <sub>90</sub>	Range	MIC <sub>90</sub>
2009	369	≤0.016-0.12	0.03	≤0.002-0.12	0.016	≤0.016-4.0	0.5	≤0.002-32.0	4.0
2010	268	≤0.016-0.25	0.06	≤0.002-0.12	0.03	≤0.016-16.0	1.0	≤0.002-32.0	32.0
2011	428	≤0.016-0.25	0.03	≤0.002-0.12	0.03	≤0.016-16.0	1.0	≤0.002-32.0	8.0
2012	494	≤0.016-0.12	≤0.016	≤0.002-0.25	0.016	≤0.016-4.0	1.0	≤0.002-32.0	4.0
2013	507	≤0.016-0.25	≤0.016	≤0.002-0.12	0.03	≤0.016-8.0	1.0	≤0.002-32.0	8.0

**AMR-Patterns among Culture Positive Cases**

Over the last five years, none of the isolates have had reduced susceptibility to cefixime or ceftriaxone (>0.25 µg/mL, Figure 4). The proportion of isolates with decreased susceptibility to azithromycin (≥2.0 µg/mL) has increased from 1.2% in 2011 and 2012 to 1.8% in 2013. The proportion of isolates resistant to penicillin (7.3%) and tetracycline (12.1%) has risen from 2012, while the proportion of isolates resistant to ciprofloxacin (14.2%) continues to remain lower than previous years.

The cefixime MIC<sub>90</sub> value has remained low at ≤0.016 µg/mL for the last two years (Table 3). However, one isolate was identified with an MIC value of 0.25 µg/mL in 2013. This isolate was collected from a heterosexual male from Calgary with an out of country contact.

An analysis of 2013 cases comparing cefixime isolates by MIC values found that isolates with a decreased susceptibility were more likely to be collected by the Calgary STI Clinic than other sites; otherwise characteristics were similar (Table 4).

The ceftriaxone MIC range (≤0.002-0.12 µg/mL) has returned to values pre-2012; while the ceftriaxone MIC<sub>90</sub> value has increased to 0.03 µg/mL (Table 3).

**Table 4. Characteristics of Culture Positive Gonorrhea Cases by Cefixime MIC values (Alberta, 2013, N=507).**

	Cefixime MIC values µg/mL n(%)		
	≤0.016 – 0.03	0.06 – 0.25	P-value
<b>N</b>	491 (96.8)	16 (3.2)	
<b>Male</b>	395 (80.4)	14 (87.5)	0.75
<b>Ethnicity</b>			
Aboriginal	95 (19.3)	0	0.07
Asian	36 (7.3)	3 (18.8)	
Black	33 (6.7)	0	
Caucasian	305 (62.1)	12 (75.0)	
Other	12 (2.4)	0	
Unknown	10 (2.0)	1 (6.3)	
<b>Reported Sexual Partners</b>			
Heterosexual	241 (49.1)	9 (56.3)	0.68
Same Sex	245 (49.9)	7 (43.8)	
<12 Not Applicable	1 (0.2)	0	
Unknown	4 (0.8)	0	
<b>Case Zone</b>			
North	11 (2.2)	0	0.11
Edmonton	263 (53.6)	4 (25.0)	
Central	8 (1.6)	0	
Calgary	199 (40.5)	11 (68.8)	
South	3 (0.6)	0	
Out of Province	7 (1.4)	1 (6.3)	
<b>Testing Agency</b>			
Calgary STI Clinic	196 (39.9)	11 (68.8)	0.06
Edmonton STI Clinic	262 (53.4)	4 (25.0)	
Other	33 (6.7)	1 (6.3)	
<b>Specimen Source</b>			
Genitourinary	283 (57.6)	12 (75.0)	0.39
Pharyngeal	110 (22.4)	3 (18.8)	
Rectal	98 (20.0)	1 (6.3)	

The range of azithromycin MIC values ( $\leq 0.016$ -8.0  $\mu\text{g/mL}$ ) has increased from the previous year, while the MIC<sub>90</sub> values have remained unchanged from 2010 (Table 3). Nine isolates (1.8%) in 2013 had decreased susceptibility to azithromycin; all collected between July and December. The majority of isolates were collected among males (n=8) reporting same sex partners (n=7). Isolates were collected at the Edmonton (n=6) and Calgary (n=3) STI Clinics. All isolates were susceptible to cefixime and ceftriaxone and two isolates were resistant to ciprofloxacin.

### NG-MAST Sequence Types (ST)

Over 20% (n=449) of isolates collected between 2009 and 2013 had NG-MAST sequencing completed (Figure 8). 157 different ST were identified and the majority (61.1%, n= 96) of the ST were unique to a single isolate. The majority of isolates identified each year are new to the Alberta data set (Table 5).

The most prevalent ST (>5 isolates) in 2013 were ST-5985 (n=21) and ST-6734 (n=10), both new ST to the Alberta data set in 2013 (Figure 9). ST-2400 (n=9) and ST-4709 (n=8) were also prevalent. Other sequence types, with less than 5 base pairs difference, were combined with the most prevalent ST from 2013 to create ST groups (Table 6). Over one-quarter (27.6%, n=124) of isolates belonged to one of the four ST groups.

From 2009-2013, the most common ST group, ST-3116 (n=75), was predominantly found in Edmonton (62.7%) although isolates of this ST group were reported from all zones of the province throughout all five years. This ST group had the largest proportion of Aboriginal people (58.7%) of all the ST groups and was predominantly spread through heterosexual activity (88.0%). All isolates were susceptible to cefixime, ceftriaxone and azithromycin, and resistant to ciprofloxacin (Table 7).

The second largest ST group was ST-5985 (n=24). Nearly two-thirds of these isolates were collected from MSM (87.5%) and isolates were reported primarily in Calgary (75.0%). These isolates were susceptible to cefixime, ceftriaxone, azithromycin and ciprofloxacin, with intermediate resistance to penicillin and resistance to tetracycline.

Table 5. Characteristics of Sequence Types (Alberta, 2009-2013, N=449)

	Year Received				
	2009	2010	2011	2012	2013
# isolates ST	59	81	88	90	131
# of different ST	24	34	42	43	55
# of new ST	-	27	31	31	44
% of ST that are new ST	-	79.4	73.8	72.1	80.0

Figure 8: Culture Positive Cases and Proportion of Cases with Sequence Typing Complete (Alberta, 2009-2013, N=2,066)

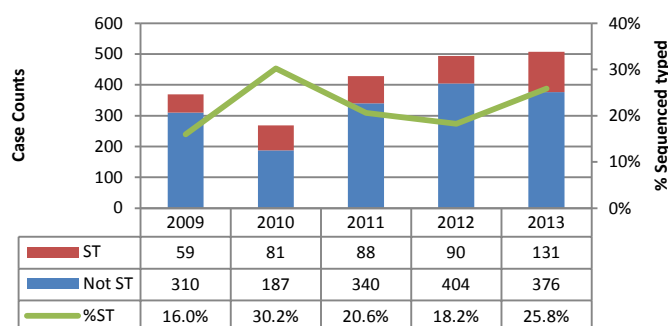


Figure 9: Isolate Count by Sequence Type by Year for ST with >5 isolates (AB, 2009-2013, N=233)

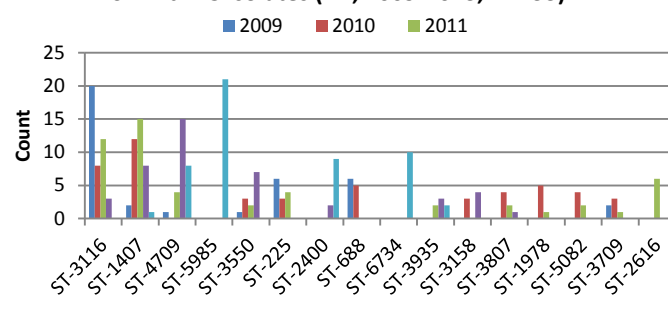


Table 6. Neisseria gonorrhoeae multi antigen sequence typing groups based on porB and tbpB sequence similarity for 2013 ST with >10 isolates (AB, N=124).

NG-MAST Group	n	Predominant ST (n)	STs which differ by $\leq 1\%$ for
			porB ST (n)
3116	75	3116 (43)	4709 (28), 5019 (2), 5362 (1), 6305 (1)
5985	24	5985 (21)	6968 (3)
2400	15	2400 (11)	6308 (1), 8030 (1), 8503 (1), 10128 (1)
6734	10	6734 (10)	-

The third largest ST group was ST-2400 (n=15). The majority of isolates were collected from MSM (86.7%) but were evenly distributed between Calgary and Edmonton. All isolates were susceptible to cefixime and ceftriaxone, with one isolate having decreased susceptibility to azithromycin. All isolates were resistant to ciprofloxacin. Isolates from this ST group were first identified in Alberta in 2011 with the majority (80.0%) being collected in 2013.

The fourth largest ST group, ST-6734 (n=10) was identified solely in 2013. The majority of isolates were collected from the Edmonton STI Clinic and were transmitted primarily through heterosexual contact. All isolates were susceptible to cefixime, ceftriaxone and azithromycin, while being resistant to ciprofloxacin.

Table 7. Characteristics of *Neisseria gonorrhoeae* Cases by NG-MAST groups (AB, 2009-2013, N=124)

	Sequence Type Group n(%)			
	3116 (75)	5985 (24)	2400 (15)	6734 (10)
<b>Testing Agency</b>				
Calgary STI Clinic	17 (22.7)	19 (79.2)	8 (53.3)	1 (10.0)
Edmonton STI Clinic	46 (61.3)	5 (20.8)	7 (46.7)	8 (80.0)
Other	12 (16.0)	0	0	1 (10.0)
<b>Gender</b>				
Male	48 (64.0)	24 (100)	15 (100)	9 (90.0)
Female	27 (36.0)	0	0	1 (10.0)
<b>Ethnicity</b>				
Aboriginal	44 (58.7)	0	0	3 (30.0)
Caucasian	20 (26.7)	19 (79.2)	15 (100)	6 (60.0)
Other	6 (8.0)	5 (20.8)	0	0
Unknown	5 (6.7)	0	0	1 (10.0)
<b>Sexual Activity</b>				
Heterosexual	66 (88.0)	2 (8.3)	1 (6.7)	8 (80.0)
WSW	1 (1.3)	0	0	0
MSM	3 (4.0)	21 (87.5)	13 (86.7)	1 (10.0)
Bisexual	2 (2.7)	1 (4.2)	1 (6.7)	0
Unknown	3 (4.0)	0	0	1 (10.0)
<b>Zone</b>				
South	1 (1.3)	0	0	0
Calgary	17 (22.7)	28 (75.0)	8 (53.3)	1 (10.0)
Central	3 (4.0)	1 (4.2)	0	0
Edmonton	47 (62.7)	5 (20.8)	6 (40.0)	8 (80.0)
North	5 (6.7)	0	1 (6.7)	1 (10.0)
Out of Province/Country	2 (2.7)	0	0	0
<b>Minimum Inhibitory Concentration</b>				
Cefixime >0.25 µg/mL	0	0	0	0
Ceftriaxone >0.25 µg/mL	0	0	0	0
Azithromycin ≥ 2.0 µg/mL	0	0	1 (6.7)	0
Ciprofloxacin Resistance	75 (100)	0	15 (100)	10 (100)
Penicillin Resistance	3 (4.0)	0	0	0
Tetracycline Resistance	0	24 (100)	0	0
<b>Received Year</b>				
2009	23 (30.7)	0	0	0
2010	9 (12.0)	0	0	0
2011	17 (22.7)	0	1 (6.7)	0
2012	18 (24.0)	3 (12.5)	2 (13.3)	0
2013	8 (10.7)	21 (87.5)	12 (80.0)	10 (100)

### Treatment Data

Provincial guidelines for the treatment of gonorrhea were updated in early 2012. Preferred treatment for MSM and pharyngeal infections was ceftriaxone 250 mg IM as a single dose (SD) plus azithromycin 1 gm po SD. Preferred treatment for heterosexuals and pregnant women was cefixime 800 mg po SD plus azithromycin 1 gm po SD.

Treatment data for uncomplicated gonorrhea cases among patients  $\geq 14$  years of age diagnosed in 2013 was available for 1,711 cases. The majority (95.9%, n=330) of MSM and pharyngeal cases were treated according to guidelines (Table 6). 82.8% (n=1,132) of heterosexual or pregnant cases received a preferred or alternate treatment. The majority of cases not receiving treatment according to the guidelines, received cefixime 400 mg which was the previously recommended treatment.

### Summary

In Alberta, there have been no gonococcal isolates with decreased susceptibility to cefixime or ceftriaxone (treatments recommended in the Alberta Treatment Guidelines for STI) between 2007 and 2013. The proportion of isolates with reduced susceptibility to cefixime (0.06 to 0.25  $\mu\text{g}/\text{mL}$ ) in 2013 has decreased to 3.2% since reaching a high in 2010 (10.1%). In addition, only one isolate with a cefixime MIC value of 0.25  $\mu\text{g}/\text{mL}$  was identified in 2013. Isolates with decreased susceptibility to azithromycin continue to be identified. NG-MAST data continues to demonstrate the diversity of sequence types in Alberta. The most prevalent ST groups identified in 2013 were susceptible to cefixime and ceftriaxone. A limitation to our GC AMR surveillance is the lack of isolates from zones outside of Edmonton and Calgary, which may limit the generalizability of the findings to rural areas in the province. A review of treatment data showed that most cases had been treated according to the new treatment guidelines released in 2012.

Table 6. Medication Used for Treatment of Uncomplicated Gonorrhea (Alberta, 2013, N=2,016)

MSM and Pharyngeal Infections (N=344)		
Met Treatment Guidelines	Ceftriaxone 250 mg IM PLUS azithromycin 1 gm PO	255 (74.1)
	Cefixime 800 mg PO PLUS azithromycin 1 gm PO	60 (17.4)
	Azithromycin 2 gm PO	15 (4.4)
Did Not Meet Treatment Guidelines	Cefixime 400 mg PO alone	3 (0.9)
	Cefixime 800 mg PO alone	2 (0.6)
	Ceftriaxone 250 mg IM alone	4 (1.2)
	Other	5 (1.5)
Heterosexual/Pregnant Women (n=1,367)		
Met Treatment Guidelines	Cefixime 800 mg po PLUS azithromycin 1 gm PO	1084 (79.3)
	Spectinomycin 2 g IM PLUS azithromycin 1 gm PO	1 (0.1)
	Azithromycin 2 gm PO	47 (3.4)
Did Not Meet Treatment Guidelines	Cefixime 800 mg PO alone	47 (3.4)
	Ceftriaxone $\geq 250$ mg IM with or without azithromycin 1 gm PO	56 (4.1)
	Cefixime 400 mg PO with or without azithromycin 1 gm PO	92 (6.7)
	Ciprofloxacin (any dose)	9 (0.7)
	Chlamydia treatment only	26 (1.9)
	Other	5 (0.4)



### The Alberta Gonorrhoea AMR Surveillance Working Group\*

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