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Gonorrhea Antimicrobial Resistance in Alberta

Gonorrhea Antimicrobial Resistance

Alberta Gonorrhea AMR
Surveillance Working Group
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Background

Gonorrhoea remains one of the oldest infections known to man. Infections can result in significant morbidity and increase the risk of HIV transmission and acquisition.¹ The incidence of gonorrhoea in Canada has been increasing since 1998 and it is the second most common notifiable sexually transmitted infection (STI) in Canada. In 2011, the national gonorrhoea rate was 33.1 per 100,000,² while in Alberta the rate was 39.4 per 100,000,³ and increased to 53.2 per 100,000 in 2012 (Alberta Health Services, unpublished data).

Since the 1940s, gonorrhoea has developed resistance to multiple classes of antibiotics.¹ 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 have been reported in Japan.^{4,5} Similar cases have since been reported from other parts of the world.¹ The creep of minimum inhibitory concentration (MIC) to third generation cephalosporins continues to be reported in Canada (Hottes, 2013) and around the world (Mehta, 2011; CDC, 2011, Lahra, 2012). The association of certain sequence types with decreased susceptibility to cephalosporins continues to grow (Chisholm, 2011; Heymans, 2012; Camara, 2012, Unemo, 2012). In addition, concerns have arisen with the use of azithromycin monotherapy (Soge, 2012; Yuan LF, Lahra, 2012).

Due to rising rates of antimicrobial resistance (AMR) to cefixime and ceftriaxone among gonococcal isolates in Canada, national treatment guidelines were revised in December 2011 and higher doses of these antibiotics were recommended. 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.⁶

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 cases of gonorrhoea are reportable by all testing laboratories as well as testing clinicians to the designate of the provincial chief medical officer of health (Alberta Health Services [AHS] Sexually Transmitted Infections Centralized Services). 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.⁷ Isolates demonstrating resistance and isolates with cefixime MIC values of ≥ 0.06 $\mu\text{g/mL}$ (beginning in 2011) are submitted to the National Microbiology Laboratory for sequence typing.

Data and Analysis

Culture positive isolates from ProvLab during 2007-2012 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.

An extract of gonorrhoea cases during the same time period was obtained from CDRS. CDRS data was merged with the ProvLab line list by specimen number. Exclusion of specimens from 2012 is shown in Figure 1.

Criteria for interpretation of MIC values were based on Clinical Laboratory Standards Institute (CLSI) standards (Table 1).⁸ CLSI does not provide resistance levels for cefixime and ceftriaxone; any isolates with a cefixime or ceftriaxone MIC >0.25 $\mu\text{g/mL}$ would be considered nonsusceptible in this report. None of the isolates submitted between 2007 and 2012 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: 0.06 – 0.125 $\mu\text{g/mL}$, and ≤ 0.016 – 0.03 $\mu\text{g/mL}$. CLSI does not provide interpretive criteria for azithromycin; an MIC value of ≥ 2.0 $\mu\text{g/mL}$ is considered to have decreased susceptibility by the American Gonococcal Isolate Surveillance Project.⁹

An extract of all gonorrhoea cases was provided from the STI module of CDRS to compare cases confirmed by culture and nucleic-acid amplification test (NAAT). An extract of 2012 treatment data was also provided. As multiple drugs may be prescribed for gonorrhoea cases, all treatments were reviewed to identify the use of a preferred or alternate treatment regime according to the 2012 Alberta STI Treatment guidelines.

Figure 1. Data Exclusion 2012

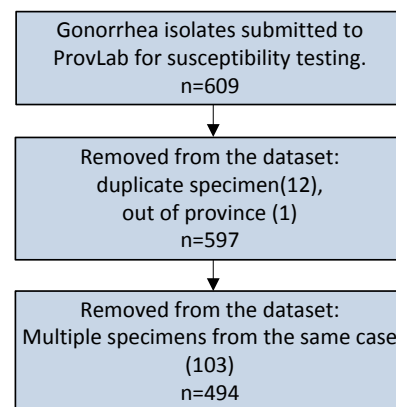
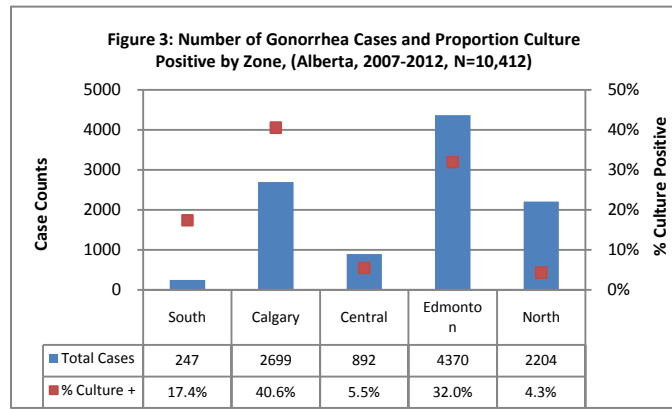
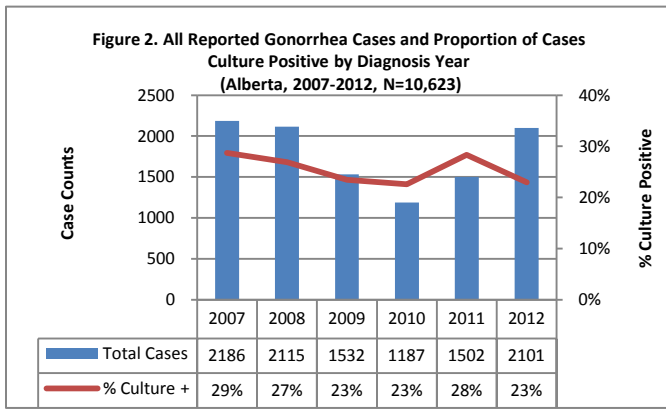


Table 1. Clinical Laboratory Standards Institute criteria for MIC Interpretations

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



P-values were calculated using chi-square or Fisher's exact test depending on cell size (excluding missing data). IBM SPSS Statistics version 19 and STATA version 10 were used to complete the analysis.

Results

Sampling of Culture Positive Cases

A total of 10,623 cases of gonorrhea were reported between 2007 and 2012 in Alberta. One-quarter of the cases (25.7%; n=2,731) were diagnosed by culture with the remainder of the cases identified through NAAT (Figure 2). The North zone has the lowest proportion of gonorrhea cases tested by culture (4.3%) while reporting 21.2% of provincial cases (Figure 3).

The majority (89.6%, n=2,448) of culture positive cases were collected from the Calgary and Edmonton STI Clinics. Therefore, cases tested by culture were more likely to be male, older, Caucasian, and report same sex partnering (Table 2).

AMR Patterns among Culture Positive Cases

A total of 2,744 culture positive isolates are available for AMR analysis over the six year period. The proportion of isolates resistant to penicillin, tetracycline and ciprofloxacin has fallen from highs recorded in previous years. None of the isolates have been resistant to cefixime or ceftriaxone (Figure 4).

Table 2. Characteristics of Gonorrhea Cases by Culture versus NAAT Methods (Alberta, 2007-2012, N=10,623).

	Test Type n(%)			p-value
	Culture	NAAT	Total	
N	2,731	7,892	10,623	
Male	1,996 (73.1)	3,928 (49.8)	5,924 (55.8)	<0.001
Median Age (IQR)	26 (21-33)	24 (20-30)	24 (20-31)	<0.001
Ethnicity (n=8,706)				
Aboriginal	640 (24.7)	3,168 (51.8)	3,808 (43.7)	<0.001
Asian	106 (4.1)	188 (3.1)	294 (3.4)	
Black	252 (9.7)	421 (6.9)	673 (7.7)	
Caucasian	1,510 (58.2)	2,205 (36.1)	3,715 (42.7)	
Other	85 (3.3)	131 (2.1)	216 (2.5)	
Reported Sexual Partnering (n=7,041)				
Heterosexual	1,634 (64.4)	4,211 (93.5)	5,845 (83.0)	<0.001
Same sex	765 (30.2)	174 (3.9)	939 (13.3)	
Bisexual	138 (5.4)	119 (2.6)	257 (3.7)	
Case Zone (n=10,412)				
North	95 (3.5)	2,109 (27.3)	2,204 (21.2)	<0.001
Edmonton	1,397 (52.1)	2,973 (38.4)	4,370 (42.0)	
Central	49 (1.8)	843 (10.9)	892 (8.6)	
Calgary	1,095 (40.9)	1,095 (40.9)	2,699 (25.9)	
South	43 (1.6)	204 (2.6)	247 (2.4)	
Testing Agency (n=10,623)				
STI Clinics	2,448 (89.6)	475 (6.0)	2,923 (26.9)	<0.001
Other Providers	283 (10.4)	7,417 (94.0)	7,700 (72.5)	

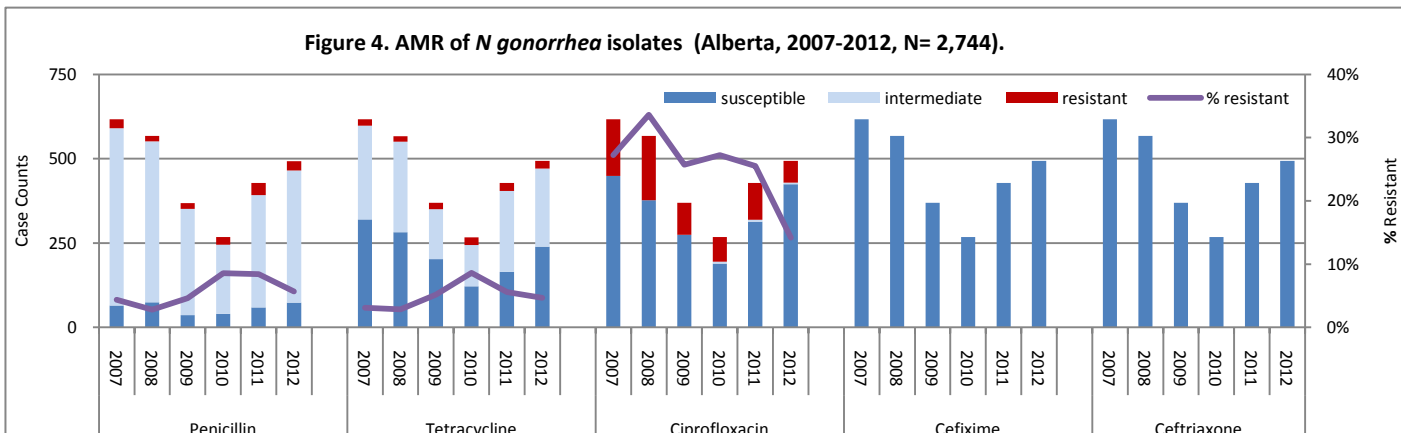


Table 3. Cefixime, Ceftriaxone and Azithromycin MIC values by Received Year (Alberta, 2007-2012, N=2,744)

Year	n	Cefixime (µg/mL)			Ceftriaxone (µg/mL)			Azithromycin (µg/mL)		
		Range	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀
2007	617	≤0.016-0.12	≤0.016	0.03	≤0.002-0.06	0.008	0.016	≤0.016-1.0	0.25	0.5
2008	568	≤0.016-0.06	≤0.016	0.03	≤0.002-0.12	0.008	0.016	≤0.016-2.0	0.25	0.5
2009	369	≤0.016-0.12	≤0.016	0.03	≤0.002-0.12	0.008	0.016	≤0.016-4.0	0.25	0.5
2010	268	≤0.016-0.25	≤0.016	0.06	≤0.002-0.12	0.008	0.03	≤0.016-16.0	0.25	1.0
2011	428	≤0.016-0.25	≤0.016	0.03	≤0.002-0.12	0.008	0.03	≤0.016-16.0	0.25	1.0
2012	494	≤0.016-0.12	≤0.016	≤0.016	≤0.002-0.25	0.008	0.016	≤0.016-4.0	0.25	1.0

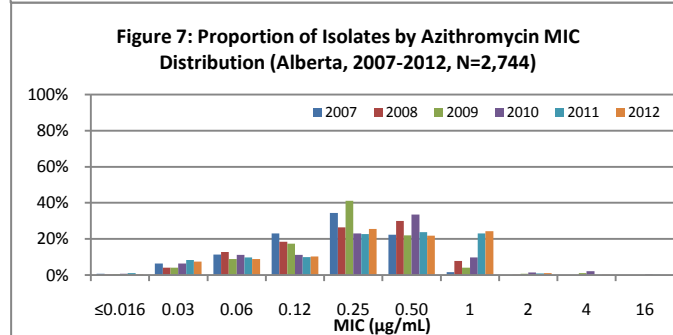
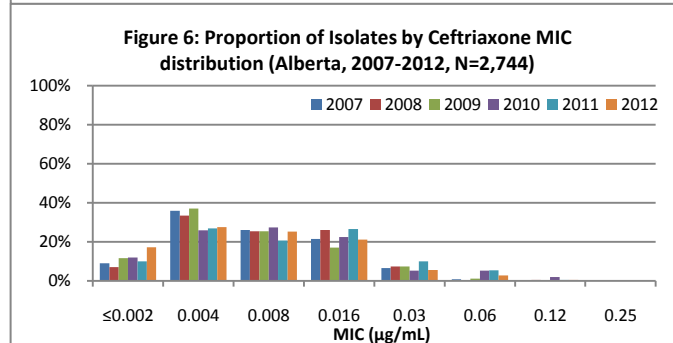
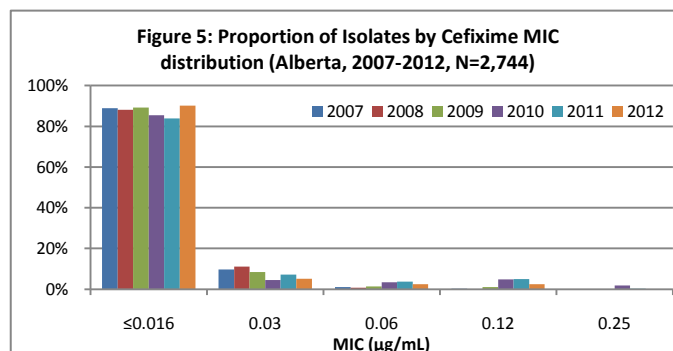
The proportion of culture positive cases with decreased susceptibility to cefixime (≥0.06 µg/mL) has changed from a low of 0.7% in 2008 to a high of 10.1% in 2010 and 4.8% in 2012 (Figure 5). The range of cefixime MIC values in 2012 has returned to 2009 values (Table 3).

An analysis of 2012 cases comparing cefixime isolates by MIC values found a significant difference in sexual partnering and testing agency (Table 4). Isolates with decreased susceptibility were more likely to involve same sex partnering and to be tested at the Calgary STI Clinic.

The ceftriaxone MIC range (≤0.002-0.25 µg/mL) has increased in 2012; although the ceftriaxone MIC₉₀ value has returned to 0.016 µg/mL (Table 3 and Figure 6). One case was identified with a ceftriaxone MIC value of 0.25 µg/mL. This isolate was collected at the Calgary STI Clinic from a heterosexual female who was positive from both the cervix and throat. The isolate was fully susceptible to cefixime and ciprofloxacin.

Table 4. Characteristics of Culture Positive Gonorrhea Cases by Cefixime MIC values (Alberta, 2012, N=494).

	Cefixime MIC values µg/mL n(%)		
	≤0.016 – 0.03	0.06 – 0.125	P-value
N	470 (95.1)	24 (4.9)	
Male	356 (75.7)	20 (83.3)	0.40
Ethnicity (n=479)			
Aboriginal	99 (21.7)	3 (13.0)	0.73
Asian	26 (5.7)	2 (8.7)	
Black	46 (10.1)	2 (8.7)	
Caucasian	270 (59.2)	16 (69.6)	
Other	15 (3.3)	0	
Reported Sexual Partnering (n=480)			
Heterosexual	270 (59.0)	8 (36.4)	0.046
Same Sex	188 (41.0)	14 (63.6)	
Case Zone			
North	10 (2.1)	1 (4.2)	0.18
Edmonton	261 (55.5)	8 (33.3)	
Central	4 (0.9)	0	
Calgary	178 (37.9)	15 (62.5)	
South	9 (1.9)	0	
Out of Province	8 (1.7)	0	
Testing Agency			
Calgary STI Clinic	182 (38.7)	15 (62.5)	0.04
Edmonton STI Clinic	250 (53.2)	7 (29.2)	
Other	38 (8.1)	2 (8.3)	
Specimen Source			
Genitourinary	299 (63.6)	11 (45.8)	0.20
Pharyngeal	96 (20.4)	9 (37.5)	
Rectal	72 (15.3)	4 (16.7)	
Other	3 (0.6)	0	



The range of azithromycin MIC values (≤ 0.016 - 4.0 $\mu\text{g/mL}$) in 2012 has returned to values found in 2009. The MIC₅₀ and the MIC₉₀ values have remained unchanged from 2010 (Table 3 and Figure 7). Six isolates (1.1%) in 2012 have decreased susceptibility to azithromycin (≥ 2.0 $\mu\text{g/mL}$). All were collected from male patients seen by an STI Clinic (Calgary n=4 and Edmonton n=2).

NG-MAST Sequence Types

NG-MAST sequence types (ST) were available for 328 isolates with the majority (78.9%; n=259) of ST being available for isolates received from 2010-2012 (Figure 8). 152 different ST were identified and nearly one-half (48.9%, n= 74) of the ST were unique to a single isolate. Nearly three-quarters of the sequence types identified each year are new (Table 5). The most prevalent ST for all years combined remains ST-3116 (n=44) and ST-1407 (n=37, Figure 9).

The most prevalent ST in 2012 was ST-4709 (n=15) with additional isolates identified first in 2009 (n=1) and 2011 (n=4). Isolates were fully susceptible to cefixime, ceftriaxone and azithromycin, but were

resistant to ciprofloxacin. The majority of ST-4709 cases were heterosexual (all cases but 1 unknown), Aboriginal (75%, n=15), male (70%, n=14), and resided in the Edmonton zone (70%, n=14), although cases were found in all zones.

Treatment Data

Provincial guidelines for the treatment of gonorrhea were updated in early 2012. The change in treatment was communicated to healthcare providers through a letter from the chief medical officer of health dated February 2012. Preferred treatment for men who have sex with men (MSM) and pharyngeal infections was ceftriaxone 250 mg IM as a single dose (SD). Preferred treatment for heterosexuals and pregnant women were cefixime 800 mg po SD. Additionally, all cases were to be co-treated for chlamydia regardless of the chlamydia test results. Chlamydia treatment

Figure 8: Culture Positive Cases and Proportion of Cases with Sequence Typing Complete (Alberta, 2007-2012, N=2,744)

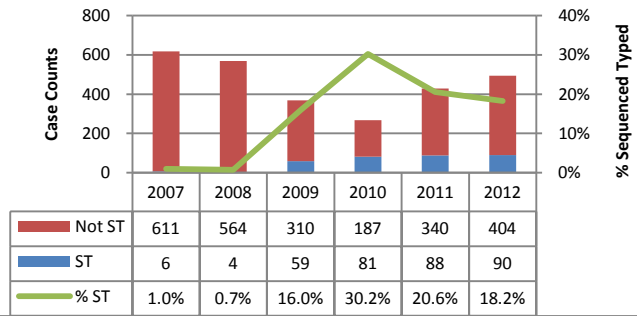


Table 5. Characteristics of Sequence Types (Alberta, 2007-2012, N=328)

	Year Received						Total
	2007	2008	2009	2010	2011	2012	
# isolates ST	6	4	59	81	88	90	328
# of different ST	6	3	24	34	42	43	152
# of new ST from previous years	-	3	21	26	31	31	118
% of new ST from previous years	-	100	88	76	74	72	78

Figure 9: Isolate Count by Sequence Type by Year for Types with >2 Isolates (AB, 2007-2012, N=206)

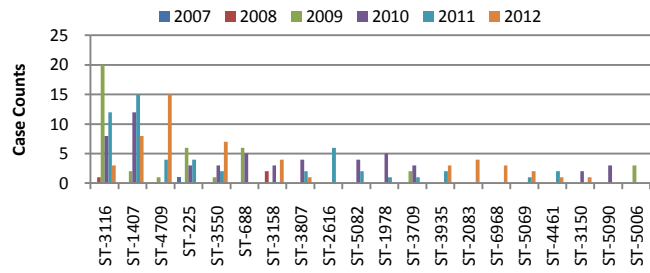


Table 6. Medication Used for Gonorrhea Treatment Among non-STI Clinic Healthcare Providers (Alberta, 2012, N=2,016)

	Medication Dose	n(%)
MSM and Pharyngeal Infections (N=319)		
Met Treatment Guidelines	Ceftriaxone 250 mg IM PLUS co-treatment for chlamydia	185 (58.0)
	Cefixime 800 mg po PLUS co-treatment for chlamydia	54 (16.9)
	Azithromycin 2 gm	3 (0.9)
Did Not Meet Treatment Guidelines	Cefixime 400 mg with or without co-treatment for chlamydia	47 (14.7)
	Cefixime 800 mg alone	12 (3.8)
	Ceftriaxone 250 mg IM alone	10 (3.1)
	Other	8 (2.5)
Heterosexual/Pregnant Women (n=1,697)		
Met Treatment Guidelines	Cefixime 800 mg po PLUS co-treatment for chlamydia	773 (45.6)
	Spectinomycin 2 g IM PLUS co-treatment for chlamydia	1 (0.06)
	Azithromycin 2 gm	43 (2.5)
Did Not Meet Treatment Guidelines	Cefixime 800 mg <u>without</u> co-treatment for chlamydia	117 (6.9)
	Ceftriaxone 250 mg IM with or without co-treatment for chlamydia	78 (4.6)
	Cefixime 400 mg with or without co-treatment for chlamydia	574 (33.8)
	Ciprofloxacin (any dose)	46 (2.7)
	Chlamydia treatment only	45 (2.7)
	Other	20 (1.2)

options include azithromycin 1 gm po SD, doxycycline 100 mg po BID x 7 days, or amoxicillin 500 mg po TID x 7 days.

Treatment data for cases diagnosed in 2012 were available for 2,016 (96.0%) cases. Three-quarters (n=242) of MSM and pharyngeal cases and nearly one-half (n=817) of heterosexual or pregnant cases received a preferred or alternate treatment (Table 6). 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 resistant to cefixime or ceftriaxone (treatments recommended in the Alberta Treatment Guidelines for STI) between 2007 and 2012. The proportion of isolates with reduced susceptibility to cefixime (≥ 0.06 $\mu\text{g}/\text{mL}$) in 2012 has decreased since reaching a high in 2010 (10.1%). In addition, no isolates with a cefixime MIC value of 0.25 $\mu\text{g}/\text{mL}$ were identified in 2012. However, Alberta's first isolate with a ceftriaxone MIC value of 0.25 $\mu\text{g}/\text{mL}$ was identified in Calgary. Isolates with reduced susceptibility to azithromycin continue to be identified. NG-MAST data continues to demonstrate the diversity of sequence types in Alberta. The most prevalent ST identified in 2012 was resistant to ciprofloxacin. 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 with a continued need to support healthcare providers in learning about the new guidelines.

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