Government of Alberta

Alberta

Alberta Health Services

2011

Gonorrhea Antimicrobial Resistance in Alberta

Gonorrhea Antimicrobial Resistance

Alberta Gonorrhea AMR Surveillance Working Group

February 2013

Background

Gonorrhea 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 gonorrhea in Canada has been increasing since 1998 and it is the second most common notifiable sexually transmitted infection (STI) in Canada. In 2010, the national gonorrhea rate was 33.4 per 100,000,[2] while in Alberta the rate was 32.0 per 100,000, and increased to 40.0 per 100,000 in 2011.[3]

Since the 1940s, gonorrhea has developed resistance to multiple classes of antibiotics.[1] Following the widespread global use of oral cephalosporins for the treatment of gonorrhea, initial reports of gonococci with reduced susceptibility and cases of treatment failure have been reported in Japan.[4,5] Similar reports have since been reported from other parts of the world.[1] In Canada, Martin et al recently reported a rise in modal minimum inhibitory concentration (MIC) in third generation cephalosporins among gonococcal isolates from 2000 to 2009.[6] In 2010, the first gonococcal isolates with MIC values of 0.25 µg/mL, the break point for cefixime resistance were reported in Alberta.

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 dosing was recommended. In February 2012, an Alberta communicable disease advisory was issued for the treatment of gonorrhea recommending cefixime 800 mg for heterosexuals and pregnant women and ceftriaxone 250 mg 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 gonorrhea 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 gonorrhea 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 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 µg/mL (beginning in 2011) are submitted to the National Microbiology Laboratory for sequence typing.

Data and Analysis

Culture positive isolates from ProvLab during 2007-2011 were extracted from the lab 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 gonorrhea 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 is shown in Figure 1.

Figure 1. Data Exclusion

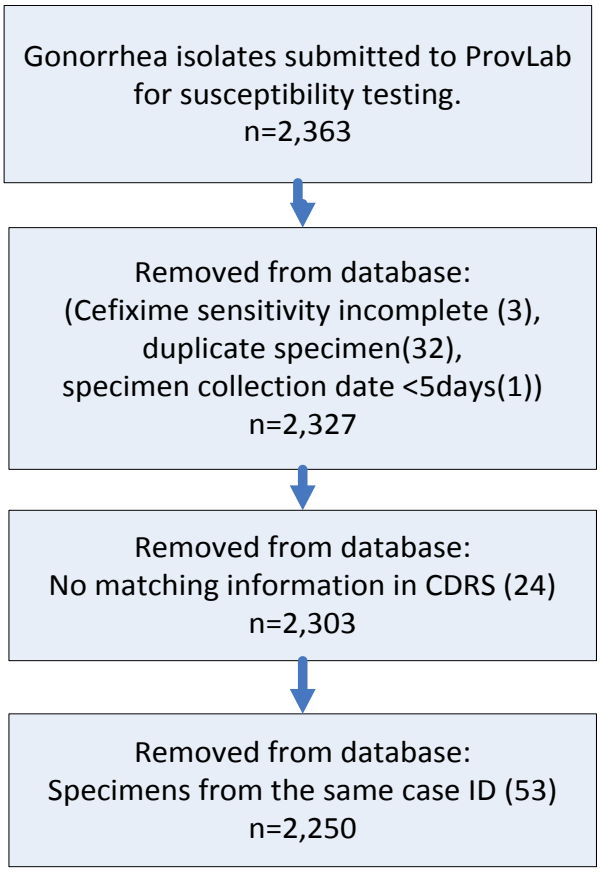


Table 1. Clinical Laboratory Standards Institute criteria for MIC Interpretations

	MIC (µg/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

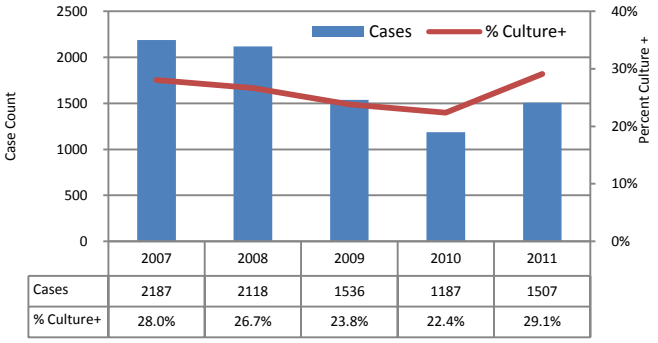
Criteria for interpretation of MIC values were based on Clinical Laboratory Standards Institute (CLSI) standards (Table 1).[8] None of the isolates submitted between 2007 and 2011 met resistance criteria for cefixime; therefore to understand characteristics associated with rising MIC values, cefixime MIC values were grouped into 3 categories: 0.25 µg/mL, 0.06 – 0.125 µg/mL, and ≤0.016 – 0.03 µg/mL. CLSI does not provide

interpretive criteria for azithromycin; an MIC value of ≥2.0 µg/mL is considered to have decreased susceptibility by the American Gonococcal Isolate Surveillance Project.[9]

An extract of gonorrhea cases was provided from the STI module of CDRS to compare culture positive cases and NAAT positive cases. An extract of treatment data was also provided. As multiple drugs are prescribed for gonorrhea cases due to the concomitant treatment of chlamydia, cases were assigned to a treatment agent based on the following hierarchy: cefixime, ceftriaxone, ofloxacin, ciprofloxacin, azithromycin and other drugs.

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

Figure 2. All Reported Gonorrhea Cases and Proportion of Cases Culture Positive by Specimen Received Year (Alberta, 2007-2011, N=8,535)



	2007	2008	2009	2010	2011
Cases	2187	2118	1536	1187	1507
% Culture+	28.0%	26.7%	23.8%	22.4%	29.1%

Table 2. Characteristics of Gonorrhea Cases by Culture versus NAAT Methods (Alberta, 2007-2011, N=8,535).

	Test Type n(%)			
N=8,535	Culture	NAAT	Total	p-value
N	2,263	6,272	8,535	
Male	1,630 (72.0)	3,176 (50.6)	4,806 (56.3)	<0.001
Median Age (IQR)	25 (21-33)	24 (20-30)	24 (20-31)	<0.001
Ethnicity (n=6,972)				
Aboriginal	546 (25.6)	2,524 (52.2)	3,070 (44.0)	<0.001
Asian	76 (3.6)	153 (3.2)	229 (3.3)	
Black	206 (9.7)	346 (7.2)	552 (7.9)	
Caucasian	1,232 (57.7)	1,721 (35.6)	2,953 (42.4)	
Other	74 (3.5)	94 (1.9)	168 (2.4)	
Reported Sexual Partnering (n=5,469)				
Heterosexual	1,348 (65.8)	3,226 (94.4)	4,574 (83.6)	<0.001
Same sex	600 (29.3)	111 (3.2)	711 (13.0)	
Bisexual	102 (5.0)	82 (2.4)	184 (3.4)	
Case Zone (n=8,368)				
North	83 (3.7)	1,612 (26.2)	1,695 (20.3)	<0.001
Edmonton	1,154 (52.0)	2,361 (38.4)	3,515 (42.0)	
Central	45 (2.0)	707 (11.5)	752 (9.0)	
Calgary	901 (40.6)	1,301 (21.2)	2,202 (26.3)	
South	38 (1.7)	166 (2.7)	204 (2.4)	
Testing Agency (n=8,535)				
STI Clinics	2,009 (88.8)	290 (4.6)	2,299 (26.9)	<0.001
Other Providers	254 (11.2)	5,982 (95.4)	6,236 (73.1)	

Results

Sampling of Culture Positive Cases

A total of 8,535 cases of gonorrhea have been reported between 2007 and 2011 in Alberta. One-quarter of the cases (n=2,263) had been tested with culture with the remainder of the cases identified through nucleic-acid amplification testing (Figure 2). The majority (88.8%, n=2,009) of culture positive cases were collected from the Calgary and Edmonton STI Clinics. Differences in culture positive cases and NAAT positive cases were identified due to the collection of cultures being concentrated to the two STI clinics. Culture positive cases were more likely to be male, Caucasian, and have reported same sex partnering as compared to NAAT positive cases (Table 2).

AMR Patterns among Culture Positive Cases

A total of 2,250 culture positive isolates are available for AMR analysis over the five year period. The proportion of isolates resistant to penicillin (ranging from 2.8% in 2008 to 8.6% in 2010 and 8.4% in 2011, p<0.001) and tetracycline (ranging from 2.8% in 2008 to 8.6% in 2010 and 5.6% in 2011, p=0.001) has changed over the five year period. Resistance to ciprofloxacin (28.3% overall; n=636) has remained consistent over time (p=0.97). None of the isolates have been resistant to cefixime or ceftriaxone (Figure 3).

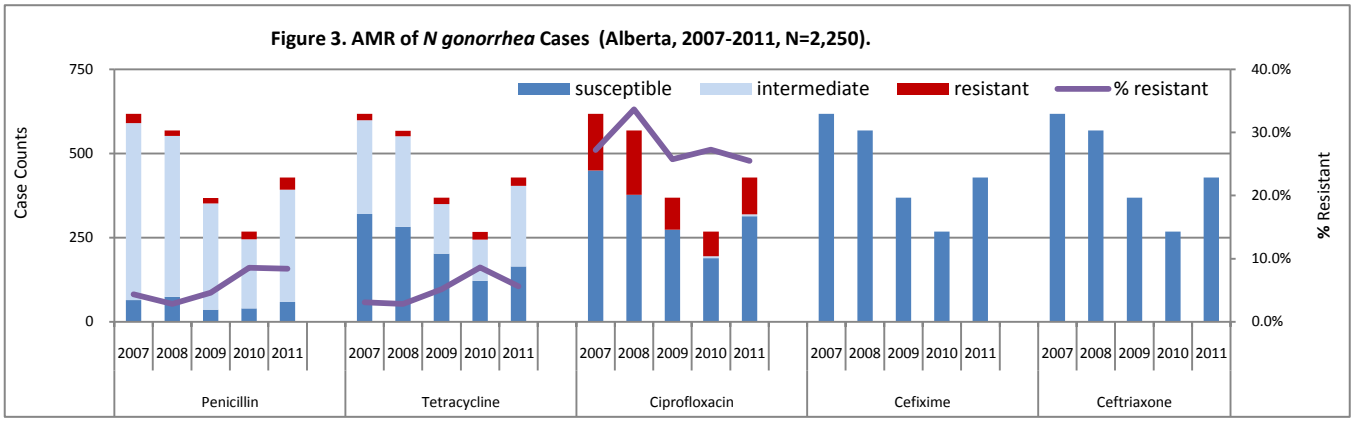


Table 3. Cefixime, Ceftriaxone and Azithromycin MIC values by Received Year (Alberta, 2007-2011, N=2,250)

		Cefixime (µg/ml)			Ceftriaxone (µg/ml)			Azithromycin (µg/ml)		
Year	n	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

The proportion of culture positive cases with reduced 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 8.9% in 2011 (p<0.001) (Figure 4). The range of cefixime MIC values in 2011 has remained unchanged from 2010 (Table 3). A pharyngeal isolate, ST-1407, with a cefixime MIC of 0.25µg/mL and cipro-resistance was observed from a heterosexual female at the Edmonton STI Clinic.

An analysis of cases by cefixime MIC values found a significant difference in the distribution of MIC values by gender, ethnicity, sexual partnering, zone and specimen type (Table 4). The proportion of cases among males, Caucasians, men who have sex with men and cases residing in Calgary increased as cefixime MIC values increased. The proportion of specimens from pharyngeal sites increased with rising MIC values as well.

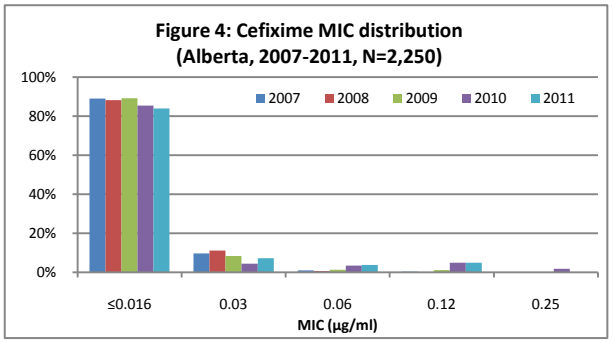
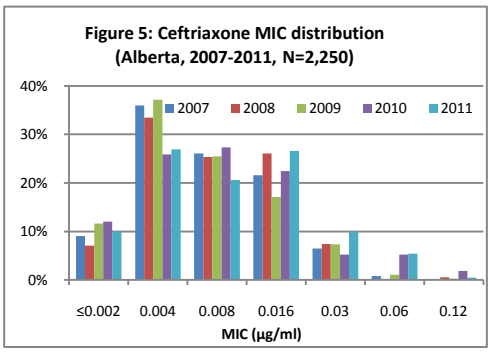


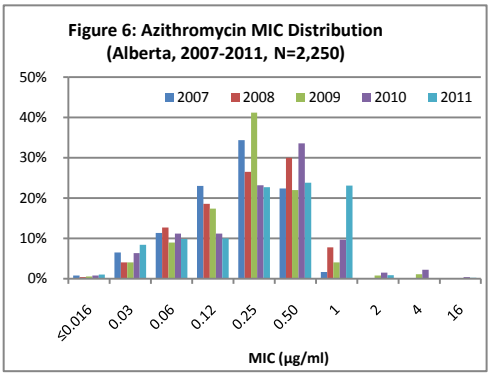
Table 4. Characteristics of Culture Positive Gonorrhea Cases by Cefixime MIC values (Alberta, 2007-2011, N=2,250).

	Cefixime MIC values µg/ml n(%)			
	≤0.016 – 0.03	0.06 – 0.125	0.25	p-value
N	2,164 (96.2)	80 (3.6)	6 (0.3)	
Male	1,555 (71.9)	70 (87.5)	5 (83.3)	0.003
Ethnicity (n=2,108)				
Aboriginal	532 (26.2)	2 (2.7)	0	<0.001
Asian	72 (3.6)	6 (8.0)	0	
Black	202 (10.0)	4 (5.3)	0	
Caucasian	1152 (56.8)	59 (78.7)	5 (83.3)	
Other	69 (3.4)	4 (5.3)	1 (16.7)	
Reported Sexual Partnering (n=2,044)				
Heterosexual exclusively	1,321 (67.4)	20 (26.0)	1 (16.7)	<0.001
Men with men	602 (30.7)	55 (71.4)	5 (83.3)	
Women with women	38 (1.9)	2 (2.6)	0	
Case Zone (n=2,209)				
North	81 (3.8)	0	0	0.03
Edmonton	1106 (52.0)	34 (44.2)	1 (16.7)	
Central	46 (2.2)	2 (2.6)	1 (16.7)	
Calgary	845 (39.7)	41 (53.2)	4 (66.7)	
South	48 (2.3)	0	0	
Testing Agency (n=2,250)				
Calgary STI Clinic	841 (38.9)	41 (51.3)	5 (83.3)	0.06
Edmonton STI Clinic	1059 (48.9)	32 (40.0)	1 (16.7)	
Other	264 (12.2)	7 (8.8)	0	
Specimen Source (n=2,249)				
Genitourinary	1,586 (73.3)	36 (45.0)	1 (16.7)	<0.001
Pharyngeal	288 (13.3)	25 (31.3)	4 (66.7)	
Rectal	266 (12.3)	19 (23.8)	1 (16.7)	
Other	23 (1.1)	0	0	

The ceftriaxone MIC range (≤0.002-0.12 µg/mL) has remained unchanged for the last four years. The ceftriaxone MIC_{90} value in 2011 (0.03 µg/mL) remained unchanged from 2010 (Table 3 and Figure 5).

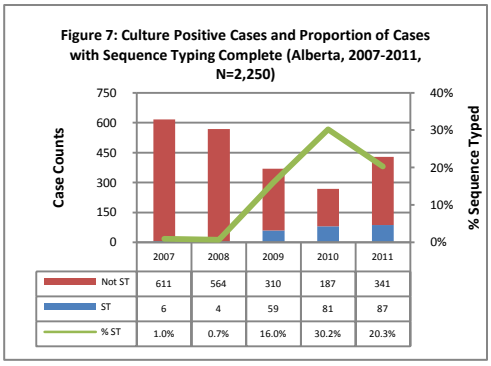
The range of azithromycin MIC values (≤0.016-16.0 µg/mL) and MIC_{90} value (1.0 µg/mL) in 2011 has remained unchanged from 2010 (Table 3 and Figure 6). Twenty-four isolates (1.1%) have reduced susceptibility to azithromycin (≥2.0 µg/mL). There was no significant gender, zone or sexual partnering difference between those with reduced susceptibility and susceptible isolates. Two gonococcal isolates with azithromycin MIC values of 16.0µg/mL were reported in 2010 and 2011. The 2010 urethral isolate was reported by the Edmonton STI Clinic from a symptomatic male who was positive from multiple sites. The 2011 pharyngeal isolate was reported by the Calgary STI Clinic from a symptomatic male. Both isolates in 2010 and 2011 had cefixime MIC values of ≤0.016 µg/mL and were susceptible to ceftriaxone and ciprofloxacin. Both clients were treated with cefixime 400mg and azithromycin 1gm and were negative on test of cure.





NG-MAST Sequence Types

NG-MAST sequence types (ST) were available for 238 isolates with the majority (95.8%; n=228) of ST being available for isolates received from 2009-2011 (Figure 7). 87 different ST were identified and 55 isolates (23.5%) had unique ST.



Through the phylogenetic reconstruction of concatenated sequences of por and tbpB alleles for prevalent STs, three clusters of isolates were identified. Cluster A occurred predominantly among male cases who reported same sex partnering and had the highest median cefixime MIC values (Table 5). This cluster includes ST-1407 (54.7%; n=29) which has been reported in other gonorrhea cases with reduced susceptibility to cephalosporin around the world[10] and across Canada.[11]

Cluster B was a predominantly heterosexual cluster with the majority of cases reported from the Edmonton zone with the highest prevalence in 2009. The predominant ST was 3116 (71.9%, n=41).

Cluster C was almost exclusively among males with the majority reporting same sex partnering. The majority of cases were reported from the Edmonton zone and were ST-225 (n=14; 36.8%).

Table 5. Characteristics of Sequence Typed Clusters (Alberta, 2007-2011, N=148)

	Cluster n(%)			
	A	B	C	p-value
N	53	57	32	
Male	46 (86.8)	39 (68.4)	31 (96.9)	**0.001**
Sexual Partnering				
Heterosexual	11 (21.2)	46 (92.0)	8 (26.7)	**<0.001**
MSM	39 (75.0)	1 (2.0)	22 (73.3)	
WSW	2 (3.8)	3 (6.0)	0	
Median Cefixime MIC µg/mL (IQR)	0.12 (0.06-0.12)	≤0.016 (≤0.016-≤0.016)	≤0.016 (≤0.016-≤0.016)	**<0.001**
Zone				
Calgary	25 (47.2)	19 (33.3)	11 (34.4)	0.61
Edmonton	23 (43.4)	32 (56.1)	17 (53.1)	
Other	5 (9.4)	6 (10.5)	4 (12.5)	
Specimen Received Year				
2007	1 (1.9)	0	1 (3.1)	**0.01**
2008	2 (3.8)	1 (1.8)	0	
2009	6 (11.5)	23 (40.4)	6 (18.8)	
2010	25 (48.1)	14 (24.6)	12 (37.5)	
2011	18 (34.6)	19 (33.3)	13 (40.6)	

Treatment Data

Treatment data from healthcare providers other than the three STI clinics was reviewed. 1,029 cases of gonorrhea were reported by healthcare providers other than the three clinics in 2011 and treatment data is available for 934 (90.8%) cases. The majority of cases (89.4%, n=835) received a dose of a recommended treatment agent (includes cefixime 400 or 800 mg, ceftriaxone 125 or 250 mg). An additional 5.8% (n=54) of cases were treated with ciprofloxacin 500 mg and 3.1% (n=29) of cases were treated solely with azithromycin. Other drugs used for the treatment of gonorrhea included doxycycline (n=9), ofloxacin (n=3), cefoxitin (n=2), metronidazole (n=1), and clindamycin (n=1). There were no significant differences between those treated with medications in the treatment guidelines and those not by gender (p=0.62) or zone (p=0.26).

Table 6. Medication Used for Gonorrhea Treatment Among non-STI Clinic Healthcare Providers (Alberta, 2011, N=934)

	Medication Dose	n(%)
Met Treatment Guidelines	Cefixime 400mg	805 (86.2)
	Cefixime (alternate dose)*	3 (0.3)
	Ceftriaxone 125 mg	5 (0.5)
	Ceftriaxone 250 mg	22 (2.4)
Did Not Meet Treatment Guidelines	Ciprofloxacin 500 mg	54 (5.8)
	Azithromycin 1 gm	25 (2.7)
	Azithromycin 2 gm	4 (0.4)
	Other	16 (1.7)

* 2 cases were treated with 800 mg among males in early 2012. 1 case received pediatric dosing.

Summary

In Alberta, there have been no gonococcal isolates resistant to cefixime or ceftriaxone (treatments recommended in the Alberta Treatment Guidelines for STI (2008) between 2007 and 2011. However, the proportion of isolates with reduced susceptibility to cefixime (≥0.06 µg/mL) has changed over time with only 0.7% of isolates with MIC ≥0.06 µg/mL in 2008 rising to 10.1% in 2010 and 8.8% in 2011. In 2010, five cases were reported at the threshold for successful treatment (12) (MIC values of 0.25µg/mL) with an additional case identified in 2011. NG-MAST typing indicates the presence of heterogeneous strains of gonorrhea in the province with clustering of strains by sexual preference and geography. A review of treatment data showed excellent adherence to provincial treatment guidelines for gonorrhea with 89.4% of cases being treated with a preferred or alternate treatment agent. These findings highlight the need for ongoing surveillance for AMR in gonorrhea in Alberta.

The Alberta Gonorrhea AMR Surveillance Working Group	
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the Alberta Gonorrhea AMR Surveillance Working Group
Special thanks to Irene Martin from the National Microbiology Laboratory
for her assistance with the sequence typing data.

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