Government of Alberta

Alberta

Alberta Health Services

Review of Gonorrhea Antimicrobial Resistance in Alberta: 2007 – 2010

March 2012

Review

Gonorrhea Antimicrobial Resistance

Background

Gonorrhea remains one of the oldest infections known to man. Infections can result in significant morbidity in males and females 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 2009, the national gonorrhea rate was 33.1 per 100,000 (2), while in Alberta the rate was 42.5 per 100,000 (3).

Since the 1940s, gonorrhea has developed resistance to multiple classes of antibiotics (1). Due to rising rates of antimicrobial resistance (AMR) to ciprofloxacin among gonococcal isolates in Canada, ciprofloxacin was removed as the first line recommended treatment for gonorrhea in the 2006 version of the national treatment guidelines for STI. Alberta switched to oral cephalosporin antibiotics in MSM in November 2005 and for all cases in May 2007 (4).

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 (5, 6). 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 (7).

In light of these observations, a review of the epidemiology of AMR in gonococcal isolates collected through Alberta's established surveillance system (4) is proposed. Our previous data demonstrated an initial rise in ciprofloxacin resistance in gonorrhea in men who have sex with men (MSM) with eventual spread to heterosexual persons prompting changes to provincial treatment guidelines. This pattern highlights the need to examine both trends in AMR as well as demographic and behavioural characteristics of the cases.

Purpose

The purpose of this analysis was:

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.

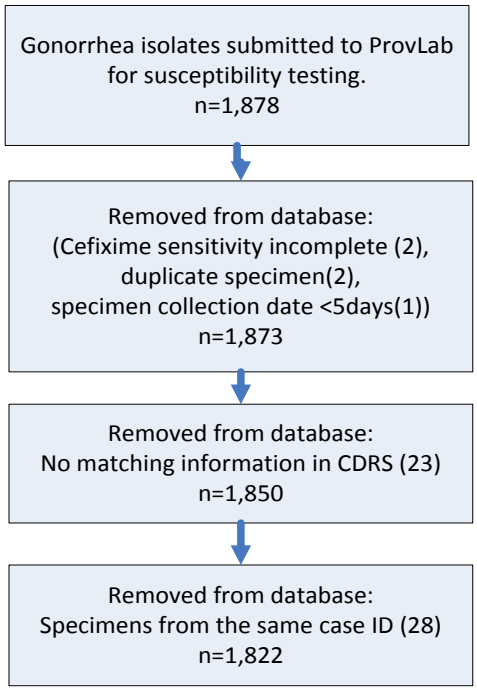
Methods

Under Alberta's Public Health Act, all cases of gonorrhea are reportable by all testing laboratories as well as testing clinicians to the provincial (Alberta Health Services [AHS]) Sexually Transmitted Disease 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 Etests 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 (8).

Data and Analysis

Specimens sent to ProvLab for gonorrhea culture from 2007-2010 were extracted from the lab database. If multiple specimens were received from the same client on the same collection day, the specimen with the most resistant pattern was chosen for inclusion. 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



Criteria for interpretation of MIC values were based on Clinical Laboratory Standards Institute standards (see Table 1). None of the isolates submitted between 2007 and 2010 have met resistance criteria for cefixime (the current drug of choice for the treatment of gonorrhea); 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. P-values were calculated using Fisher's exact test (excluding missing data). Linear by linear association was used to assess differences across time. SPSS version 19 and STATA version 10 were used to complete the analysis.

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

An extract of treatment data was provided from the STI module of CDRS. 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, spectinomycin, ciprofloxacin, and other drugs.

Results

A total of 7,077 cases of gonorrhea have been reported between 2007 and 2010 in the province of Alberta. Gonorrhea AMR is available for 1,822 (25.7%) of the total cases (Figure 2). Overall, 86.4% (n=1,575) of isolates were collected from either the Calgary or Edmonton STI Clinics. Over the four year period, there has been a decline in the number of positive isolates collected from other testing agencies (p<0.001, Table 2).

Thirty per cent (n=562) of culture positive isolates were resistant to at least one antibiotic and this has remained consistent over the 4 year period (p=0.77). The proportion of isolates resistant to penicillin (4.4% in 2007 and 8.6% in 2010, p=0.01) and tetracycline (3.1% in 2007 to 8.6% in 2010, P<0.001) has increased over the 4 year period. Resistance to ciprofloxacin (28.9% overall; n=527) has remained consistent over time (p=0.61). None of the isolates have been resistant to cefixime or ceftriaxone (Figure 3).

Figure 2. Reported Gonorrhea Cases and Proportion Culture Positive by Specimen Received Year (Alberta, 2007-2010)

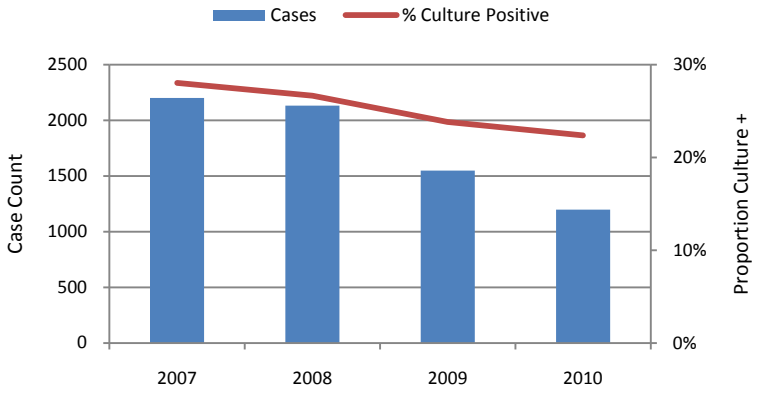
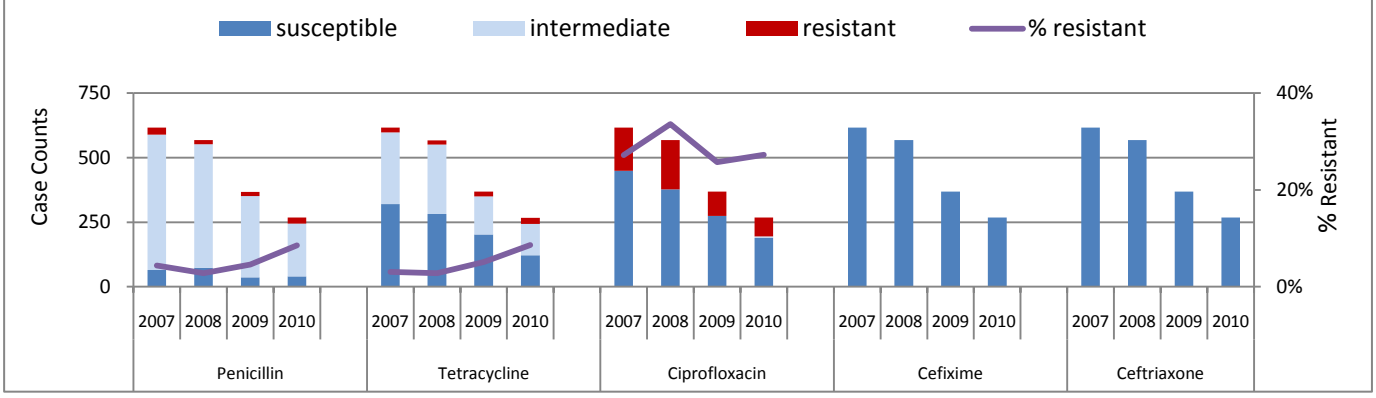


Table 2. Culture Positive Isolates by Testing Agency and Specimen Received Year (Alberta, 2007-2010)

N=1,822	Specimen Received Year n(%)				
Testing Agency	2007	2008	2009	2010	Total
Calgary STI Clinic	267 (43.3)	208 (36.6)	133 (36.0)	116 (43.4)	724 (39.7)
Edmonton STI Clinic	237 (38.4)	275 (48.4)	199 (53.9)	140 (52.2)	851 (46.7)
Other Agency	113 (18.3)	85 (15.0)	37 (10.0)	12 (4.5)	247 (13.6)
Total	617	568	369	268	1822

Figure 3. AMR of *N gonorrhea* isolates (Alberta 2007-2010).



The proportion of culture positive cases with reduced susceptibility to cefixime (≥0.06 µg/ml) increased in 2010 to 10.7% of isolates in comparison to 1.3% in 2007(p<0.001). In addition in 2010, the range of MIC values has increased to its widest range in the four year period and the MIC_{90} value has risen for the first time in four years (Table 3). 2010 marked the first year that cases with MIC values of 0.25µg/ml were found (n=5, Figure 4).

The ceftriaxone MIC_{90} value rose for the first time in 2010 from 0.016µg/ml in 2007 to 2009 to 0.03µg/ml (Table 3). The range of MIC values has remained consistently between <0.002-0.12 µg/ml over the last three years (Figure 5).

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

Characteristics of Cases with Cefixime MIC value of 0.25 µg/ml (n=5)

Five cases had cefixime MIC values of 0.25µg/ml. The cases were all among men, 80% were Caucasian, 80% resided in the Calgary zone, and all reported some same sex activity. All were tested at the Calgary STI Clinic during 2010 and all specimens were resistant to ciprofloxacin as well. Specimen sites included; throat (n=3), rectal (n=1), and urethra (n=1). Two of

Figure 4. Cefixime MIC distribution (Alberta, 2007-2010)

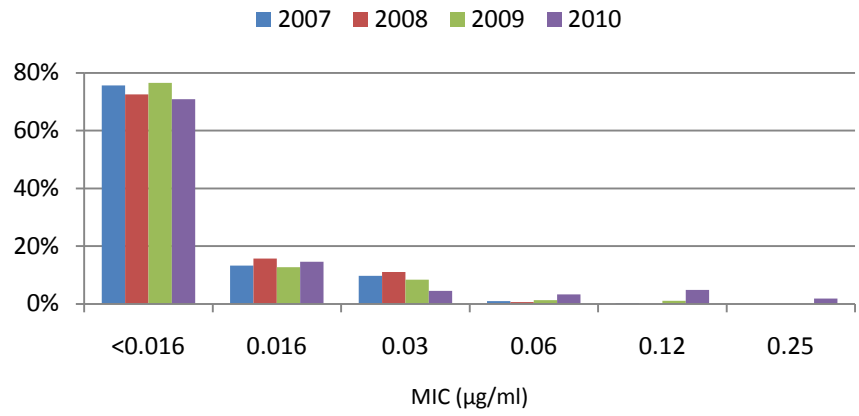
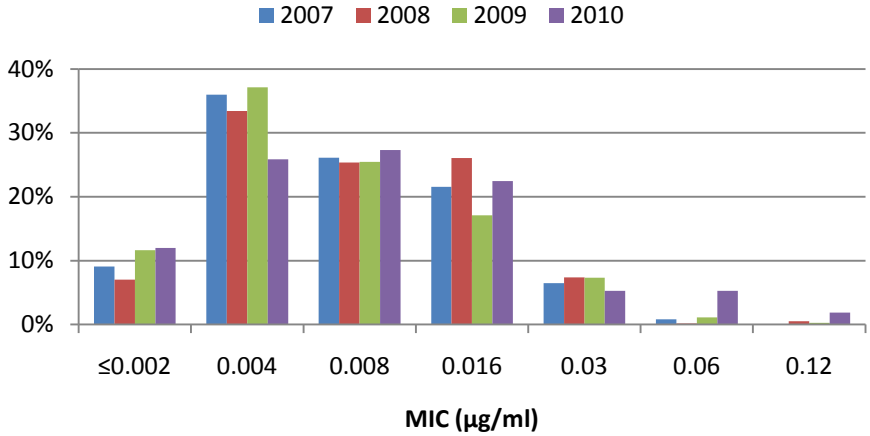


Table 3. Cefixime and Ceftriaxone MIC values by Received Year (Alberta, 2007-2010)

N=1,822		Cefixime (µg/ml)			Ceftriaxone (µg/ml)		
Year	n	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
2008	568	<0.016-0.06	<0.016	0.03	<0.002-0.12	0.008	0.016
2009	369	<0.016-0.12	<0.016	0.03	<0.002-0.12	0.008	0.016
2010	268	<0.016-0.25	<0.016	0.06	<0.002-0.12	0.008	0.03

Figure 5. Ceftriaxone MIC distribution (Alberta, 2007-2010)



the cases reported travel outside of Canada. Contacts to the cases were either anonymous or outside of the country. Four of the cases were NG MAST typed as ST1407 which has also been reported in other gonorrhea cases with reduced susceptibility to cephalosporin around the world (9) and across Canada (personal communication, Irene Martin, National Microbiology Laboratory). The remaining case (sex only in Calgary) was ST3149, although 2 months prior the case had been infected with ST1407.

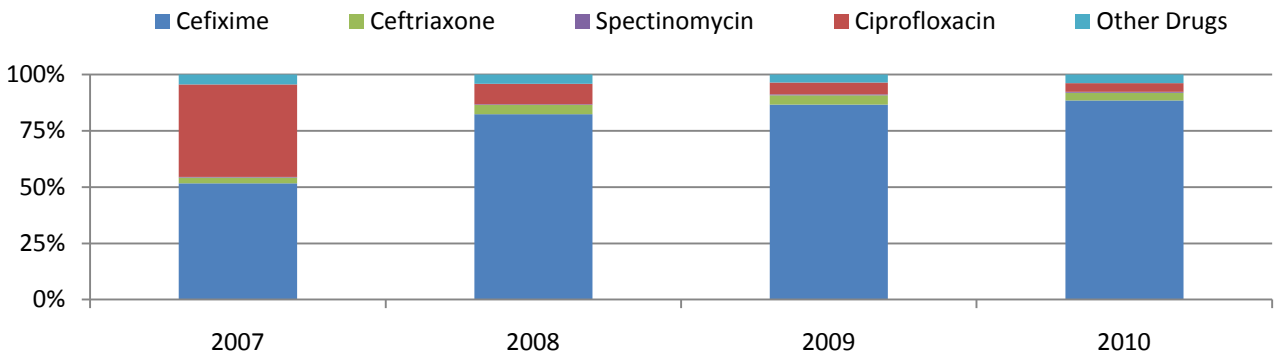
Treatment Data

Treatment data is available for 6,660 (94.1%) of reported cases between 2007 and 2010. The majority of cases (95.9%, n=6,390) received a dose of a recommended treatment agent (includes cefixime, ceftriaxone, spectinomycin, or ciprofloxacin). A shift in the use of ciprofloxacin and cefixime in 2007 and 2008 is observed as a result of the change in treatment guidelines (Figure 6). Other drugs used for the treatment of gonorrhea included azithromycin (n=172), doxycycline (n=65), ofloxacin (n=11), amoxicillin (n=6), metronidazole (n=5), clindamycin (n=4), cefoxitin (n=3), erythromycin (n=3), and ampicillin (n=1).

Table 4. Characteristics of Culture Positive Gonorrhea Cases by Cefixime MIC values (Alberta, 2007-2010).

	Cefixime MIC values µg/ml n(%)			
N=1,822	<0.016 – 0.03	0.06 – 0.125	0.25	p-value
N	1,774 (97.4)	43 (2.3)	5 (0.3)	
Male	1,252 (70.6)	40 (93.0)	5 (100)	0.001
Ethnicity (n=1,694)				
Aboriginal	451 (27.3)	1 (2.6)	0	<0.001
Asian	57 (3.5)	2 (5.3)	0	
Black	169 (10.2)	0	0	
Caucasian	916 (55.5)	33 (86.8)	4 (80.0)	
Other	58 (3.5)	2 (5.3)	1 (20.0)	
Reported Sexual Partnering (n=1,625)				
Heterosexual exclusively	1,124 (71.1)	9 (22.5)	0	<0.001
Men with men	427 (27.0)	31 (77.5)	5 (100)	
Women with women	29 (1.8)	0	0	
Case Zone (n=1,787)				
North	69 (4.0)	0	0	0.19
Edmonton	877 (50.4)	22 (52.4)	0	
Central	38 (2.2)	1 (2.4)	1 (20.0)	
Calgary	711 (40.9)	19 (45.2)	4 (80.0)	
South	45 (2.60	0	0	
Testing Agency (n=1,822)				
Calgary STI Clinic	701 (39.5)	18 (41.9)	5	0.15
Edmonton STI Clinic	832 (46.9)	19 (44.2)	0	
Other	241 (13.6)	6 (14.0)	0	
Specimen Source (n=1,820)				
Genitourinary	1,347 (76.0)	19 (44.2)	1 (20.0)	<0.001
Pharyngeal	199 (11.2)	13 (30.2)	3 (60.0)	
Rectal	204 (11.5)	11 (25.6)	1 (20.0)	
Other	22 (1.2)	0	0	

Figure 6: Proportion of Gonorrhea Cases by Treatment Agent (Alberta, 2007-2010)



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 2010. However, the proportion of isolates with reduced susceptibility (≥0.06 µg/ml) has changed over time with the widest range of MIC values being reported in 2010. In 2010, five cases (1.9%) have been reported at the break point for cefixime resistance (MIC values of 0.25µg/ml). All five of these cases involved men who have had sex with men and two of the cases reported sexual contact outside of Canada. Only 25.7% of gonorrhea cases reported in the period 2007 to 2010 were tested for antimicrobial resistance; it is therefore possible that the five reported cases are an underestimation of the number of cases at the threshold for successful treatment (10). These findings highlight the need for ongoing surveillance for AMR in gonorrhea in Alberta.

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Prepared by Jennifer Gratrix and Dr. Ameeta Singh on behalf of
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