

Resistance to Ceftriaxone and Azithromycin in *Neisseria gonorrhoeae* Isolates From 7 Countries of South America and the Caribbean: 2010–2011

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Abstract: Seven countries in Latin America and the Caribbean report on (2010 and 2011) the susceptibility of 2235 isolates of *Neisseria gonorrhoeae* to 6 antibiotics. Thirteen isolates had ceftriaxone minimum inhibitory concentrations (MICs) of 0.125 to \geq 0.25 mg/L. The percentage of resistant isolates to the following antibiotics was: azithromycin, 1.0% to 1.7%; ciprofloxacin, 42.1% to 36.2%; penicillin, 31% to 35%; tetracycline, 21.8% to 22.6%.

There were an estimated 78 million cases of gonorrhea, caused by the pathogen *Neisseria gonorrhoeae*, worldwide in 2012.¹ In the absence of an effective vaccine, gonococcal control programs rely on effective antimicrobial treatment and surveillance.² However, *N. gonorrhoeae* isolates have become resistant to every class of antimicrobial agent and can be resistant to multiple antibiotics simultaneously.^{3,4} Over the last decade, gonococcal isolates have become resistant to extended spectrum cephalosporins (ESCs), the last antibiotic class used in a single treatment dose. In response to this crisis, the World Health Organization (WHO) developed a global action plan to control the spread and impact of antimicrobial resistance (AMR) in *N. gonorrhoeae*.² The WHO emphasized the need to strengthen surveillance of gonococcal AMR regionally and internationally.² A Gonococcal Antimicrobial Surveillance Program (GASP) was established in Latin America and the Caribbean (LAC) countries during 1990s.^{5,6} Our report describes the antimicrobial susceptibility of *N. gonorrhoeae* isolates

collected in Argentina (n = 666), Bolivia (n = 30), Chile (n = 1264), Colombia (n = 88), Cuba (n = 57), Uruguay (n = 112), and Venezuela (n = 20) between 2010 and 2011.

To determine antimicrobial susceptibility, the agar dilution method was used by 3 countries (Argentina, Colombia, and Uruguay), 3 countries (Chile, Colombia, and Cuba) used E-test, and 4 (Bolivia, Chile, Colombia, and Venezuela) used the disk diffusion assay. Colombia determined susceptibility by all 3 methods and Chile performed both E-test and disk diffusion assays. Manufacturer's instructions (bioMérieux, Saint Laurent, Quebec, Canada) were followed for E-test⁷, and other methods were reported previously.⁷ The medium used for antimicrobial susceptibility testing was Difco GC Medium Base (GCMB) (Becton Dickinson, NJ) supplemented with Kellogg's medium (1%; GCMBK) or IsoVitalX (1%) (Becton Dickinson, NJ).⁷ Combinations of *N. gonorrhoeae* strains A-E, WHO III, V and VII and ATCC 49226 were reference strains for antimicrobial susceptibility testing.^{8,9} Susceptibility was classified using Clinical Laboratory Standards Institute criteria.⁷ Azithromycin resistance was defined as an MIC \geq 2 μ g/mL.¹⁰ All laboratories participated in an international quality assurance program for gonococcal susceptibility.¹¹

The susceptibility to ceftriaxone of *N. gonorrhoeae* isolates was ascertained by all countries for 2010 (n = 987) and 2011 (n = 1215) (Fig. 1). Argentina, Colombia, and Uruguay reported a 2-fold increase in MIC₅₀ to ceftriaxone (from 0.004 to 0.008 mg/L) between 2010 and 2011. In Cuba, the MIC₅₀ (0.016–0.008 mg/L) to ceftriaxone decreased by 2-fold in 2011. Overall, in 2010, one isolate with a ceftriaxone MIC of 0.25 mg/L was reported (Cuba—1/28). In 2011, 12 isolates were reported as having ceftriaxone MICs 0.125 to 0.25 mg/L; Argentina (8/350), Chile (3/725), and Uruguay (1/51). Only Argentina reported the susceptibility of *N. gonorrhoeae* isolates to cefixime (2012) which ranged from 0.001 to 0.5 mg/L. Twelve of 179 (6.7%) isolates had cefixime MICs \geq 0.125 mg/L.

Argentina, Chile, Cuba, and Uruguay determined the susceptibility of gonococcal isolates to azithromycin (Fig. 2). Aggregate resistance to azithromycin was 1.0% (6/612) in 2010 and 1.7% (20/1169) in 2011. In 2010, azithromycin-resistant *N. gonorrhoeae* isolates were noted in Argentina (1.6%, 5/316) and Uruguay (1.7%, 1/59). In 2011, azithromycin-resistant gonococci were reported from Argentina (1.4%, 5/350), Chile (0.7%, 5/725), Colombia (7.3%, 3/41), and Uruguay (13.2%, 7/53). During the reporting period, several countries reported a 2-fold change in aggregate MIC₅₀ to azithromycin: Argentina (0.25–0.5 mg/L), Colombia (0.125–0.25 mg/L), and Uruguay (0.5–0.25 mg/L). The MIC₅₀ (0.125 mg/L) remained unchanged for Chile.

All countries determined *N. gonorrhoeae* susceptibility to ciprofloxacin. Overall, ciprofloxacin resistance increased from 28.0% (285/1019) of isolates tested in 2010 to 36.2% (439/1214) in 2011 (Table 1). A decrease in ciprofloxacin resistance in 2011,

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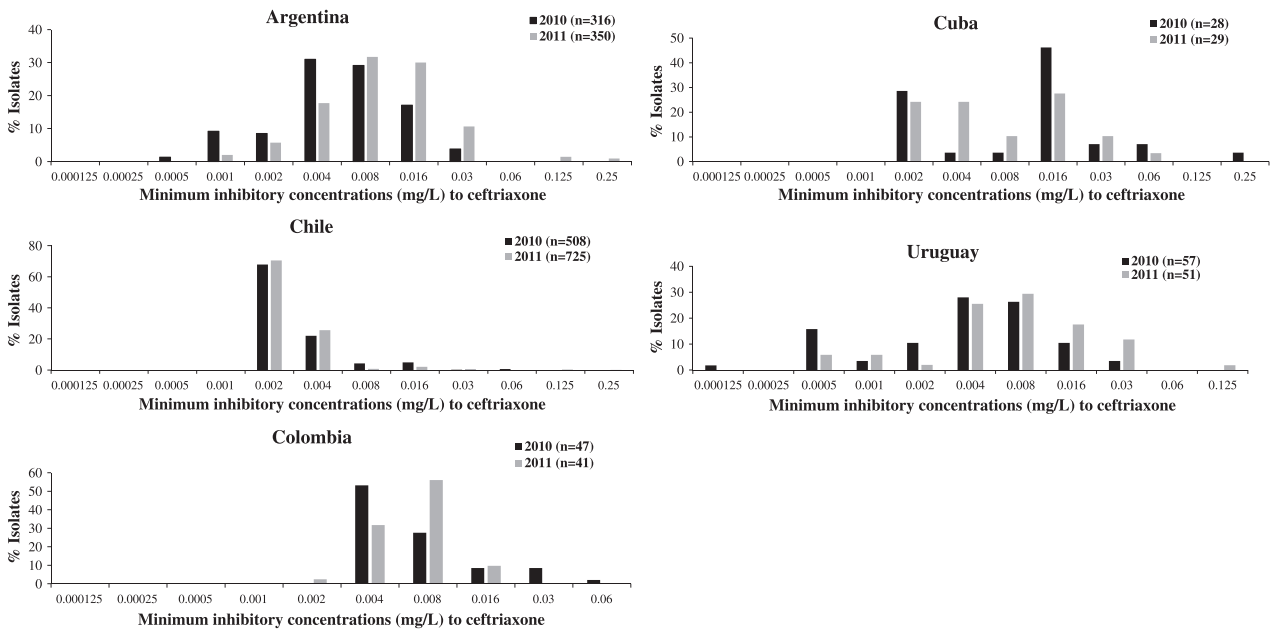


Figure 1. Trends of *N. gonorrhoeae* ceftriaxone susceptibility from 5 countries from Latin America and the Caribbean for 2010 to 2011. In total 987 and 1215 *N. gonorrhoeae* isolates were tested for ceftriaxone susceptibility for 7 countries for 2010 and 2011. This figure excludes isolates from Bolivia (n = 17, 2010; n = 13, 2011) and Venezuela (n = 14, 2010; n = 6, 2011) since isolates from these countries were tested by the disk diffusion method and MICs were not provided.

as compared with 2010, was noted in Venezuela (0/6, 0% in 2011, 3/14, 21.4% in 2010). Increases in ciprofloxacin resistance were observed in Argentina (167/350, 47.7% in 2011; 26.9%, 85/316 in 2010), Chile (31.7%, 230/725 in 2011; 29.4%, 158/538 in 2010), Colombia (34.1%, 14/41 in 2011; 25.5%, 12/47 in 2010), Cuba (14/29, 48.3% in 2010; 20/28, 71.4% in 2011), and Uruguay (28%, 14/50 in 2011; 11.9%, 7/59 in 2010).

All countries tested gonococcal isolates for susceptibility to penicillin. Aggregate penicillin resistance increased from 31.1%

(316/1016) of isolates tested in 2010 to 35.9% (436/1216) in 2011 (Table 1). Penicillin resistance increased in the following countries from 2010 to 2011: Argentina, 20.9% (66/316) of isolates tested in 2010 to 35.7% (125/350) in 2011; Chile, 32.7% (176/538) of isolates tested in 2010 to 33.5% (243/726); Colombia, 50.6% (28/47) of isolates tested in 2010 to 70.7% (29/41); and Cuba, 25% (7/28) of isolates tested in 2010 to 37.9% (11/29). Penicillin resistance decreased in Uruguay (37.5%, 21/56 in 2010; 27.4%, 14/51 in 2011). The percentage

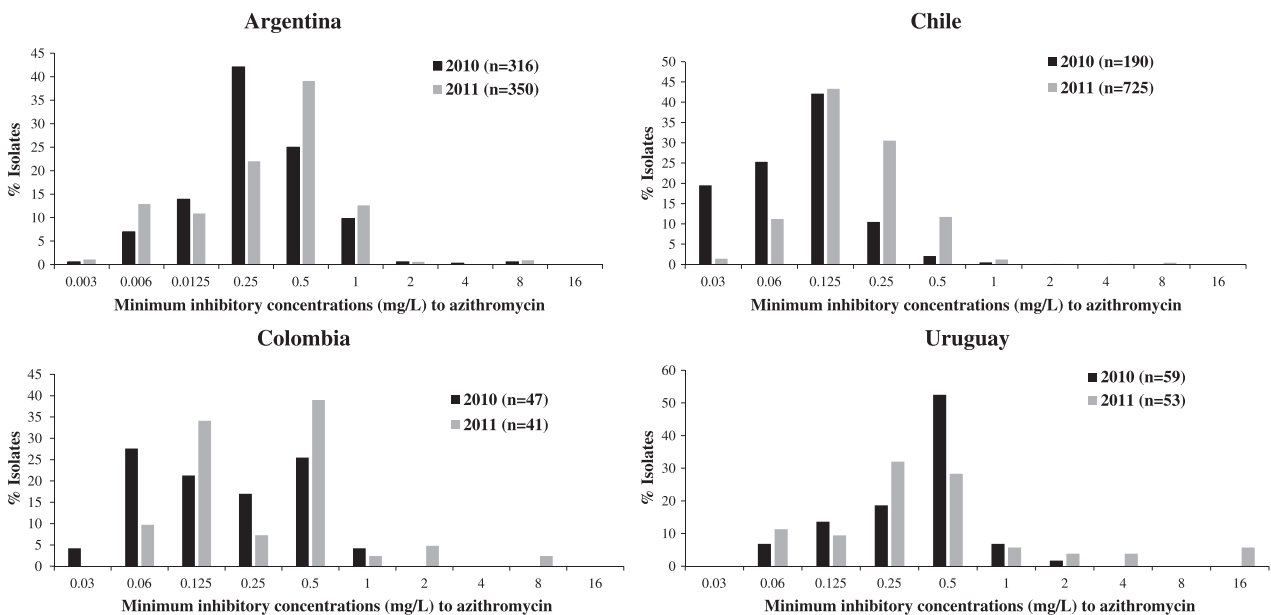


Figure 2. Trends of *N. gonorrhoeae* azithromycin susceptibility from 4 countries from Latin America and the Caribbean for 2010 to 2011. In total 621 and 1169 *N. gonorrhoeae* isolates were tested for azithromycin susceptibility for 2010 and 2011. Bolivia, Cuba, and Venezuela did not report on gonococcal azithromycin susceptibility for the period.

TABLE 1. Resistance to Penicillin, Tetracycline, and Ciprofloxacin in 6 South American Countries and Cuba, 2010–2011

Country	Number and Percentage of Resistant Isolates					
	Ciprofloxacin		Penicillin [¶]		Tetracycline ^{¶¶}	
	2010, n* (%)	2011, n (%)	2010, n (%)	2011, n (%)	2010, n (%)	2011, n (%)
Argentina	85/316 (26.9)	167/350 (47.7) [†]	66/316 (20.9)	125/350 (35.7) [†]	85/316 (26.9)	153/350 (43.7) [†]
Bolivia [‡]	0/17 (0.0)	0/13 (0.0)	11/17 (64.7)	9/13 (69.2)	6/17 (35.3)	6/13 (46.2)
Chile	158/538 (29.4)	230/725 (31.7)	176/538 (32.7)	243/726 (33.5)	37/382 (9.7)	53/724 (7.3)
Colombia	12/47 (25.5)	14/41 (34.1)	28/47 (59.6)	29/41 (70.7)	22/47 (46.8)	14/41 (34.1)
Cuba	20/28 (71.4)	14/29 (48.3)	7/28 (25.0)	11/29 (37.9)	16/28 (57.1)	10/29 (34.5)
Uruguay	7/59 (11.9)	14/50 (28.0)	21/56 (37.5)	14/51 (27.4)	21/55 (38.2)	35/53 (66.0) [†]
Venezuela [‡]	3/14 (21.4)	0/6 (0.0)	7/14 (50.0)	5/6 (83.3)	0/14 (0.0)	4/6 (66.7)
Total resistant	285/1019 (28.0)	439/1214 (36.2) [†]	316/1016 (31.1)	436/1216 (35.9) [†]	187/859 (21.8)	275/1216 (22.6)

*Number of isolates.

[†]P value < 0.05.

[‡]Antimicrobial susceptibility determined by disk diffusion.

[¶]Overall, the prevalence of penicillinase-producing *N. gonorrhoeae* (PPNG) was 7.67% (78/1016) of isolates tested in 2010 and 7.48% (91/1216) in 2011.

^{¶¶}Overall, the prevalence of presumptive tetracycline-resistant *N. gonorrhoeae* (plasmid mediated; MIC ≥16.0 mg/L) was 8.2% (70/858) of isolates tested in 2010 and 6.8% (83/1216) in 2011.

prevalence of penicillinase-producing *N. gonorrhoeae* (PPNG) isolates was stable: 7.67% (78/1016) in 2010 and 7.48% (91/1216) in 2011 overall.

The overall percentage of tetracycline resistant isolates remained stable in 2010 (21.8%, 187/858) and 2011 (22.6%, 275/1216) (Table 1). Nevertheless, the prevalence of tetracycline resistance in 2011 increased in the following countries: Argentina (26.9%, 85/316 in 2010; 43.7%, 153/350 in 2011), Bolivia (35.3%, 6/17 in 2010; 46.2%, 6/13 in 2011), Uruguay (38.2%, 21/55 in 2010; 66.1%, 35/53 in 2011), Venezuela (0%, 0/14 in 2010; 66.7%, 4/6 in 2011). Plasmid-mediated tetracycline-resistant *N. gonorrhoeae* (TRNG) prevalence in 2010 was 8.2% (70/858) and 6.8% (83/1216) in 2011.

Argentina (n = 316, 2010; n = 214, 2011), Chile (n = 131, 2010; n = 724, 2011), Colombia (n = 47, 2010; n = 41, 2011), and Cuba (n = 29, 2011) determined the susceptibility of *N. gonorrhoeae* isolates to spectinomycin. All (n = 1502) isolates were reported as susceptible (data not shown).

N. gonorrhoeae isolates with reduced susceptibility (MICs ≥0.125–0.25 mg/L) to ceftriaxone were not reported from LAC before 2007 when 7 isolates with MICs ≥0.25 mg/L were identified in Manaus, Brazil.⁵ In 2014, an isolate resistant to ceftriaxone and cefixime (MIC 0.5 mg/L) was reported from Argentina, indicating the emergence of gonococcal resistance to ESCs.¹² We determined that between 2010 and 2011, 13 isolates with ceftriaxone MICs ≥0.125 mg/L were identified in 4 countries. The low prevalence of isolates with reduced susceptibility to ESCs during this period might reflect the low level of their adoption as treatment options in the region.

N. gonorrhoeae isolates with resistance or reduced susceptibility to azithromycin were reported in Cuba and Brazil in the mid-1990s and high-level azithromycin resistance was reported in Argentina.^{6,13} Azithromycin resistance in 6 Latin American countries ranged from 6% of gonococcal isolates tested in 2000 to 23% in 2009.⁵ The present study reports a substantial decrease in the prevalence of azithromycin-resistant isolates in 2010 and 2011 as compared with previous reports.⁵ The sudden shift in trends of azithromycin susceptibility requires consistent monitoring of gonococcal susceptibility to this antimicrobial because it is currently recommended as part of the first-line treatment of gonorrhea (ceftriaxone plus azithromycin) in various countries.¹⁴

The widespread global distribution of ciprofloxacin resistance in *N. gonorrhoeae* isolates resulted in the replacement of this

antibiotic by ESCs for the treatment of gonococcal infections.^{15,16} Gonococcal quinolone resistance in Latin America and Caribbean countries was rare in the 1990s, reflecting the limited use of these antibiotics in the region at the time.⁶ Aggregate ciprofloxacin resistance in 11 reporting countries from Latin America increased from 2% in 2000 to 31% in 2009.⁵ We observed a continuation of this trend in 2010 and 2011. At the time of the present report, ciprofloxacin was the recommended first-line treatment for gonorrhea infections in several countries.^{6,17}

High rates of penicillin resistance have been reported globally for decades.^{4–6,13,18–20} The proportion of *N. gonorrhoeae* isolates with penicillin resistance in western Pacific countries/regions in 2010 ranged between 18.1% (New Zealand) and 96.7% (Thailand).¹⁸ The Euro-GASP demonstrated an overall burden of 21% penicillin resistance between 2006 and 2008.¹⁹ In the United States, the Gonococcal Isolate Surveillance Project (GISP) reported approximately 10% penicillin resistance in *N. gonorrhoeae* isolates for each year since the late 1980s.²⁰ In Latin America and the Caribbean, penicillin resistance is widespread and resistance rates remained above 20% between 1990 and 2009.^{5,6} We report similar trends for 2010 and 2011 with an increase in 2011 compared with 2010.

Tetracycline resistance overall varied between 21.8% and 61.1% of *N. gonorrhoeae* isolates tested between 1990 and 2011 in LAC with the overall percentage of resistant isolates remaining above 21% throughout the surveillance period.^{5,6} Euro-GASP reported a tetracycline resistance prevalence of 60% between 2006 and 2008.¹⁹ In the Western Pacific regions, the proportion of tetracycline-resistant *N. gonorrhoeae* has remained high for many years with a range of 10% to 100% of isolates tested.¹⁸

Spectinomycin is used as an alternative regimen for treating urogenital gonorrhea in patients who do not tolerate cephalosporins.²¹ High levels of resistance developed when this antimicrobial was used in Korea in the mid-1980s.²² All *N. gonorrhoeae* isolates tested in 2010 from the United States were susceptible to spectinomycin.²³ Gonococcal isolates (12 or less) with in vitro resistance or decreased susceptibility to spectinomycin have been sporadically reported from some Asian countries.¹⁸ All *N. gonorrhoeae* isolates from 2000 through 2009, tested for antimicrobial susceptibility to spectinomycin from 5 LAC countries were susceptible.⁶ Similar trends were observed for 2010 and 2011.

This report presents antimicrobial susceptibility data from 7 countries of Latin America and the Caribbean. A major limitation

identified during this study was the lack of the current WHO reference strain panel for antimicrobial susceptibility testing. This difficulty has since been rectified. Most concerning is the reality that several countries in LAC are no longer able to perform AMR surveillance due to budgetary restrictions and declining expertise in isolating, culturing and testing isolates from patients. The development of non-culture-based methods to ascertain AMR is becoming ever more urgent to develop realistic, timely, and effective guidelines for treatment.

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