Retrospective Analysis of Antimicrobial Susceptibility Trends (2000–2009) in *Neisseria gonorrhoeae* Isolates from Countries in Latin America and the Caribbean Shows Evolving Resistance to Ciprofloxacin, Azithromycin and Decreased Susceptibility to Ceftriaxone

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Background: The emergence of resistance and treatment failures to third generation cephalosporins prompted the revitalization of the global Gonococcal Antimicrobial Surveillance Program (GASP) to ensure that information regarding trends of the antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates is up-to-date. Accordingly, former and potential GASP participants in Latin America and the Caribbean were contacted to reinitiate the GASP network in the region and to undertake a retrospective analysis of the antimicrobial susceptibility of *N. gonorrhoeae* isolates between 2000 and 2009.

Methods: Eleven countries participated in this retrospective analysis reporting on the susceptibility of *N. gonorrhoeae* isolates to up to 6 antibiotics as well as national treatment guidelines over the period. Antimicrobial susceptibility determination was carried out using combination of agar dilution and disk diffusion (Clinical Laboratory and Standards Institute) or Etest. Antimicrobial susceptibility data from each country were aggregated and analyzed for antimicrobial resistance trends in the region.

Results: More than 11,400 *N. gonorrhoeae* isolates were tested for antimicrobial susceptibility: 6 countries tested *N. gonorrhoeae* over the entire period and 5 countries tested sporadically. Decreased susceptibility to ceftriaxone was reported from 1 country (7 isolates, MICs >0.25 μg/ml) in 2007. No resistance to spectinomycin was reported. From 2000 to 2009, aggregated ciprofloxacin resistance increased from 2% (19/784) to 31% (311/1015) in 9 countries and azithromycin resistance increased from 6% (39/646) to 23% (225/962) in 4/6 reporting countries. Overall, resistance to penicillin and tetracycline decreased from 35% (441/1241) to 26% (258/975) and from 60% (476/792) to 35% (323/931), respectively.

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In 2009, resistance to gentamicin (3%, 4/122), chloramphenicol (5%, 6/120), and ofloxacin (2%, 6/120) was reported from 1 country.
Conclusions: The report of ceftriaxone-resistant isolates coupled with the emergence and spread of resistance to ciprofloxacin and azithromycin in Latin America and the Caribbean in the 2000s indicates the importance of active surveillance of *N. gonorrhoeae* antimicrobial susceptibility to determine antimicrobial resistance emerging trends so as to promptly inform and guide the development of effective treatment options for gonococcal infections.

The enduring expansion of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* isolates to antibiotics used for the treatment of gonococcal infections makes it essential that the timely evaluation of trends in gonococcal antimicrobial susceptibility be on-going.[1,2] The selective pressure exerted by antimicrobial agents used for the treatment of infections caused by *N. gonorrhoeae* has historically contributed to the assorted AMR trends that have been observed ever since the introduction of sulfonamides in the 1930s.[3] Currently, extended spectrum cephalosporins, including ceftriaxone and the oral antibiotic cefixime, represent the ultimate single-dose therapeutic option for the treatment of gonococcal infections, as well as being the first choice for the treatment of gonorrhea in most countries.[4–6] Because effective antimicrobial therapy remains a pillar for the control of gonococcal infections, the emergence of strains that are resistant to or have decreasing susceptibility to third-generation cephalosporins,[7–9] coupled with increasing reports of treatment failure to oral cephalosporins, such as cefixime,[10–13] presents serious public health challenges. For this reason, the World Health Organization (WHO) is working to actively promote global *N. gonorrhoeae* antimicrobial susceptibility surveillance programs (GASP) to establish what antimicrobials remain effective as treatment for infections caused by *N. gonorrhoeae*. Several countries have revised their treatment guidelines in consideration of the increasing percentage of *N. gonorrhoeae* isolates with decreased susceptibility to third-generation cephalosporins.[14–16]

The evaluation of potential alternative drugs alone or in combination to treat gonococcal infections is being considered. In particular, the susceptibility of *N. gonorrhoeae* isolates in Europe to gentamicin has been recently reported[17] and its use in combination therapy with azithromycin is presently under investigation.[18]

In countries in Latin America and the Caribbean (LAC), gonorrhea infection is a serious problem and up-to-date information is largely lacking. Furthermore, for a number of reasons, including country-based limited resources, antimicrobial susceptibility surveillance of *N. gonorrhoeae* is often compromised, and data on AMR are warranted. An active GASP in LAC countries was established during 1990s.[19–23] Information about trends of the susceptibility to different antimicrobial agents was periodically reported from 41 countries (including the Caribbean region).[24] Results were used to inform public health policy such as updating treatment guidelines in various countries to reflect antibiotics to which *N. gonorrhoeae* was susceptible.[24] Regrettably, lack of sustained funding for these activities during the 2000s curtailed active international surveillance.

Although ciprofloxacin still represents one of the first-line therapies recommended in guidelines for the treatment of uncomplicated gonorrhea infections in many countries, some (e.g., Chile, Costa Rica, Mexico, and Panama) no longer recommend ciprofloxacin as reported in a recent study.[25] Few studies during the 1990s reported on trends in ciprofloxacin resistance in these countries, although *N. gonorrhoeae* isolates with decreased susceptibility were identified, and some resistant isolates were reported from Cuba,[26,27] and from Argentina in 2001.[28] However, resistance to ciprofloxacin was not endemic in these countries. The present retrospective study describes antimicrobial susceptibility of *N. gonorrhoeae* isolates evaluated from 11 LAC countries from 2000 to 2009. The purpose of the study was to encourage countries to analyze and report data that had been collected but remained "in the drawer" and to ascertain the trends in susceptibility to various antimicrobials both presently recommended for treatment as well as to penicillin and tetracycline, antimicrobials used for treatment in the past. These results reveal the emergence of high percentages of *N. gonorrhoeae* isolates resistant to ciprofloxacin and azithromycin over the period. Further, a few isolates with MICs reflecting decreased susceptibility to ceftriaxone (>0.25 μg/ml) were reported from 1 country.

MATERIALS AND METHODS

Participating Countries and Data Collection

To reinitiate GASP-LAC activities, a survey was undertaken in 2009 to determine interest in participating in GASP-LAC Phase 2 activities and to determine what methods and activities had been undertaken during the 2000s pertaining to *N. gonorrhoeae* identification and antimicrobial susceptibility. Laboratory groups that had participated in GASP-LAC phase 1 activities were contacted by the GASP-LAC Coordinating Centre (University of Saskatchewan, Saskatoon, Canada). They were also asked to identify possible new participants from countries that had not previously been able to engage in the GASP program. Although contacts covered 41 countries, 11 countries indicated an active interest and ability to immediately participate in GASP-LAC Phase 2 activities; 20 countries, represented by 1 contact, i.e., the Caribbean Epidemiology Centre [(CAREC); the Caribbean community supports CAREC to improve the health status of the Caribbean people] and 9 countries from Central America and Mexico were unable to participate or reported no infrastructure enabling AS testing of *N. gonorrheae*.

Gonococcal antimicrobial susceptibility surveillance had been conducted at various levels (i.e., national, local, on-going, sporadic) in 11 countries. Nine of these countries had previously participated in GASP-LAC Phase 1 programs.[24] They maintained the Clinical Laboratory and Standards Institute (CLSI) recommended antimicrobial susceptibility and identification methods adopted in GASP-LAC Phase 1[1,24,29,30] countries (Paraguay and Ecuador) were new to the network.

Countries were asked to retrospectively analyze trends in *N. gonorrhoeae* antimicrobial susceptibility between 2000 and 2009 and report the number and percentage of *N. gonorrhoeae* isolates that were classified as being Susceptible (S), Intermediate (I), or Resistant (R) to the antibiotics tested or showing decreased susceptibility to ceftriaxone using criteria described later. Information regarding current national treatment guidelines for gonorrhea alone was also reported by 9 countries. Data were submitted and presented orally during a Workshop to reinitiate the GASP, which was held in Buenos Aires, Argentina (November 2–4, 2010) to review *N. gonorrhoeae* antimicrobial susceptibility trends in LAC.[31] Data were subsequently aggregated and analyzed at the GASP-LAC Coordinating Centre and each participating country confirmed reported data on multiple occasions.

Quality Assurance Among GASP-LAC Members

To ascertain the comparability of data between countries, collected during the 2000s, a structured questionnaire regarding the methods used for the identification and antimicrobial

TABLE 1. Number of *N. gonorrhoeae* Isolates Tested by Country and Year in South America and Cuba, 2000–2009

	No Isolates Tested*										
Country†/yr	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**Total**
Argentina	323	340	507	482	644	394	346	253	295	310	3894
Bolivia	114	54	45	35	18	16	22	26	31	13	374
Brazil	455	655	486	305	230	202	128	278	77	120	2936
Chile	244	281	267	232	126	358	335	398	412	463	3116
Colombia	17	28	11	4	12	9	9	12	7	25	134
Cuba	—	—	—	—	—	—	—	40	40	40	120
Ecuador	—	—	—	—	—	—	—	—	—	7	7
Peru	35	35	20	—	—	221	40	—	—	—	351
Uruguay	27	31	24	18	26	19	9	23	25	44	246
Venezuela	32	37	31	87	69	23	12	15	15	—	321
Total	1247	1461	1391	1163	1125	1242	901	1045	902	1022	11,499

*The number of isolates reported in this table indicates the highest number of isolates tested in each country during the study period.
†Data from Paraguay not included as only percentages were reported.

susceptibility testing of *N. gonorrhoeae* isolates, including reference strains, was circulated to prospective GASP Phase 2 participants. Results were reported to and analyzed by the GASP-LAC Coordinating Centre and were also discussed during the GASP meeting in Buenos Aires, 2010.[31] Notably, GASP continuity was realized since GASP Phase 1 as several personnel active in and trained (laboratory-based training courses at the GASP Coordinating Centre for Latin America and the Caribbean in 1994 and 1997, and at CAREC in 1995) during that period continued to lead the GASP effort in their countries.[24] Also, during the 2000s, a quality assurance (QA) program was conducted in some LAC countries building on the QA program established for GASP Phase 1 (Aurora Maldonado, personal communication; data unpublished).

Identification of *N. gonorrhoeae* and Antimicrobial Susceptibility Testing

Isolates collected in each country were confirmed to be *N. gonorrhoeae* by a number of standard methods including Gram stain, oxidase test, carbohydrate utilization tests, and Gonogen II test (New Horizons Diagnostics, Columbia, MD, USA) (data presented at the 19th Biennal conference for the International Society for Sexually Transmitted Diseases Research (ISSTDR) [P1-S4.28], Quebec City, Canada).

Antimicrobial susceptibility testing methods included minimum inhibitory concentration (MIC) determination by agar dilution and Etest (bioMérieux, Saint Laurent, Quebec, Canada). Also AMR determination was ascertained using disk diffusion alone, or coupled with agar dilution or Etest. Standard procedures according to CLSI and Etest manufacturer's instructions were adopted.[24,29,30]

The medium used for antimicrobial susceptibility testing in all countries was GC Medium Base (GCMB) (Difco, Becton Dickinson, Franklin Lakes, NJ) supplemented with Kellogg's medium (1%) or IsoVitaleX (1%) (Becton Dickinson, Franklin Lakes, NJ). For agar dilution, MIC testing GCMB was supplemented with serial 2-fold dilutions of penicillin (MIC range 0.032–256.0 μg/ml), tetracycline (0.064–32.0 μg/ml), ciprofloxacin (0.001–16.0 μg/ml), ceftriaxone (0.000125–0.5 μg/ml), azithromycin (0.008–32.0 μg/ml), and/or spectinomycin (4.0–256.0 μg/ml). Disc potencies were 10 units for penicillin, 30 μg for tetracycline, 5 μg for ciprofloxacin, and 30 μg for ceftriaxone, as recommended by CLSI.[29] Other antimicrobials such as chloramphenicol, erythromycin and ofloxacin, and gentamicin were additionally tested by Etest in Brazil.

Reference strains used varied among countries and included *N. gonorrhoeae* ATCC 49,226 (as recommended by CLSI) alone or coupled with *N. gonorrhoeae* strains WHO III, V, VII or *N.*

TABLE 2. Number of *N. gonorrhoeae* Isolates Tested by Country and Antibiotic in South America and Cuba, 2000–2009

Country*/Antibiotic	**Ciprofloxacin**	**Azithromycin**	**Ceftriaxone**	**Spectinomycin**	**Penicillin†**	**Tetracycline‡**
Argentina	**3894**	3894	3894	3894	3894	3894
Bolivia	**374**	0	374	0	374	374
Brazil§	712	635	712	0	**2936**	712
Chile	**3116**	3116	3116	3116	3116	3116
Colombia	**134**	134	134	134	134	134
Cuba	**120**	0	120	0	0	0
Ecuador	**7**	0	7	0	7	0
Peru	**351**	351	311	351	351	351
Uruguay	237	**243**	242	169	236	200
Venezuela	**321**	0	321	0	321	303
Total	9266	8373	9231	7664	11,369	9084

Bold values indicate the highest number of isolates tested in each country irrespective of antibiotic.
*Data from Paraguay not included as only percentages were reported.
†Countries reporting penicillinase-producing *N. gonorrhoeae* (PPNG) include Argentina (566/3894); Bolivia (147/374); Brazil (644/2936); Chile (822/3116); Colombia (64/134); Peru (64/351); and Uruguay (15/236).
‡Countries reporting tetracycline-resistant *N. gonorrhoeae* (TRNG) include Argentina (179/3894); Chile (448/3,116); Colombia (40/134); Peru (114/351); and Uruguay (6/200).
§Brazil also tested gentamicin, chloramphenicol, and ofloxacin.

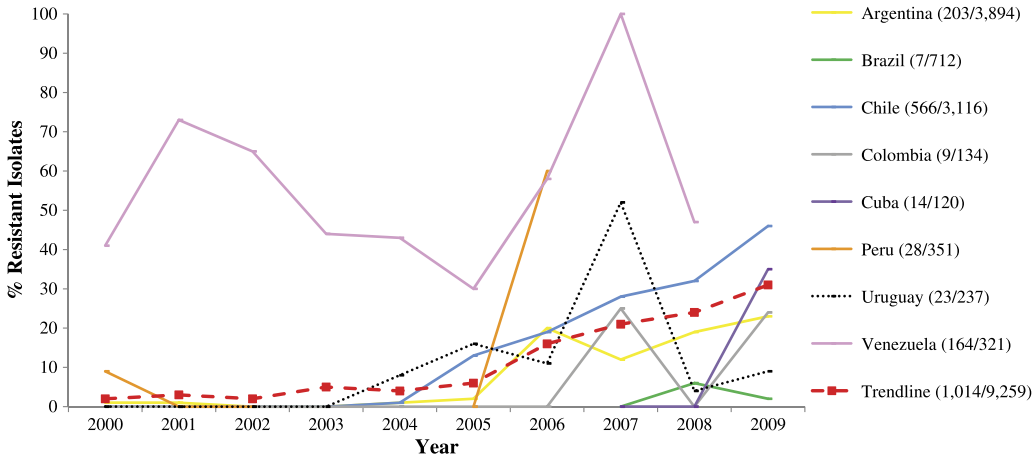

Figure 1. Trends in percentages of ciprofloxacin resistant *N. gonorrhoeae* isolates in 7 countries* in South America and Cuba. *In Bolivia (n = 374) no isolates resistant to ciprofloxacin were identified.

gonorrhoeae strains WHO A-E. In addition to *N. gonorrhoeae* ATCC 49,226, some countries (n = 2) also reported using *Staphylococcus aureus* ATCC 25,923 (or ATCC 29,213) and *Escherichia coli* ATCC 25,922. The newer panel of recommended reference strains was not available over the period of testing.[32] Categorization of DS, R, I, and S was based on CLSI criteria.[29] Breakpoints for other antibiotics tested were based on published criteria for resistance as follows: azithromycin (MIC ≥ 2 μg/ml),[33,34] chloramphenicol (MIC = 2 μg/ml),[34] erythromycin (MIC = 4 μg/ml),[35] ofloxacin (MIC = 2 μg/ml),[29]and gentamicin (MIC = 32 μg/ml).[35]

Antimicrobial susceptibility testing to penicillin, tetracycline, ciprofloxacin, and ceftriaxone was performed in 9 countries. Argentina, Bolivia, Chile, and Colombia tested these antimicrobials over the entire study period. Brazil reported data for 2001, February 2002-June 2003 (considered as 2002), 2004, 2007, 2008, and 2009. Paraguay reported data between 2006 and 2009 and Peru for 2000–2002, 2005, and 2006. Uruguay tested for β-lactamase production to ascertain penicillin resistance in 2009 and did not report on tetracycline antimicrobial susceptibility in 2009. Venezuela did not report on tetracycline antimicrobial susceptibility in 2007 or for any agent in 2009. Cuba tested ciprofloxacin and ceftriaxone antimicrobial susceptibility between 2007 and 2009, and Ecuador tested ciprofloxacin, ceftriaxone, and penicillin antimicrobial susceptibility only in 2009.

Susceptibility to azithromycin and spectinomycin was tested in Argentina, Chile, and Colombia, over the entire study period; in Uruguay between 2000 and 2007; and in Peru between 2000–2002, 2005, and 2006. Brazil reported on azithromycin susceptibility, in 2001, 2004, 2007, and 2009 and also tested *N. gonorrhoeae* antimicrobial susceptibility to chloramphenicol, erythromycin, ofloxacin in 2001, 2004, 2007, and 2009 (chloramphenicol susceptibility was also tested in 2002) and gentamicin in 2009.

Pencillinase-producing *N. gonorrhoeae* (PPNG) isolates were identified in 7 countries using the chromogenic cephalosporin assay according to the manufacturer's instructions.[24] Salvador (Bahia) Brazil reported only PPNG results, and these data were included with aggregated penicillin resistance results. Plasmid-mediated resistance to tetracycline (tetracycline-resistant *N. gonorrhoeae* [TRNG]) was specifically reported in 5 countries based on MIC values of ≥16 μg/ml.

Statistical Analysis

Statistical significance was assessed using the χ^2 test. $P < 0.05$ was considered significant.

RESULTS

From 2000 to 2009, a total of 11,499 *N. gonorrhoeae* isolates were tested for antimicrobial susceptibility in the region

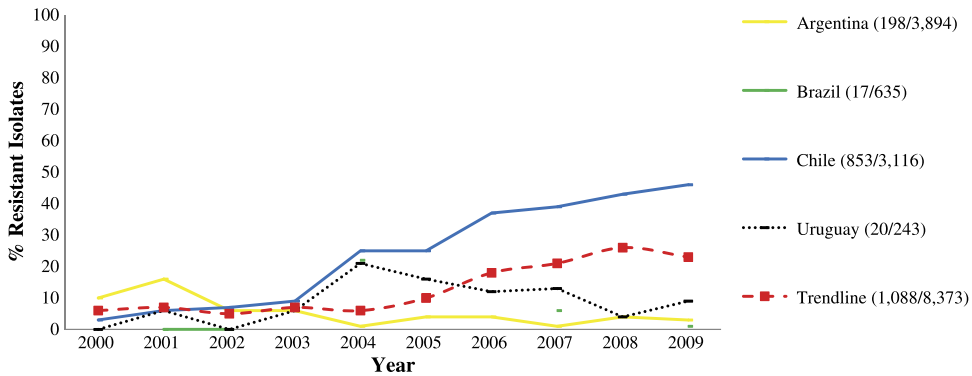

Figure 2. Trends in percentages of azithromycin resistant *N. gonorrhoeae* isolates in 4 countries* in South America, 2000–2009. *In Colombia (n = 134) and in Peru (n = 351) no isolates resistant to azithromycin were identified.

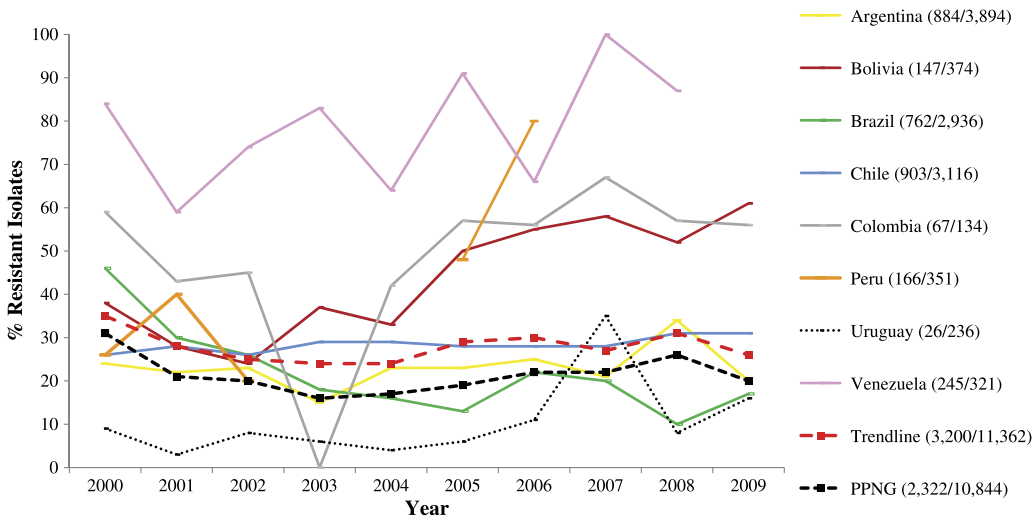

Figure 3. Trends in percentages of penicillin resistant *N. gonorrhoeae* isolates in 8 countries in South America, 2000–2009.

(Table 1). The total number of isolates tested over the period in each reporting country ranged from 120–3894 (Table 1), and the total number of isolates tested by year ranged from 1461 in 2001 to 901 in 2006 (Table 1). The number of *N. gonorrhoeae* isolates tested susceptibility to each antibiotic also varied (Table 2), i.e., 9231 isolates for ceftriaxone, 7664 for spectinomycin, 9266 for ciprofloxacin, 8373 for azithromycin, 11,369 for penicillin, and 9084 for tetracycline.

Isolates With Decreased Susceptibility to Ceftriaxone and Susceptibility to Spectinomycin

All *N. gonorrhoeae* isolates tested for antimicrobial susceptibility to ceftriaxone (9231) were essentially susceptible in all reporting countries (n = 11). The exception was a report from Manaus, Brazil, where 6% (7/120) of isolates tested in 2007 had MICs >0.25 μg/ml, and a zone diameter of inhibition disk <35 mm (data not shown) indicating decreased susceptibility.

All *N. gonorrhoeae* isolates tested for antimicrobial susceptibility to spectinomycin (7664) were susceptible in all reporting countries (n = 5) (Table 2). In Colombia, 2 of 25 isolates tested in 2009 showed intermediate resistance (MIC = 64 μg/ml) to spectinomycin (data not shown).

Resistance to Ciprofloxacin Emerges in Most Countries During the Mid 2000s

Ciprofloxacin resistance was detected in all but 1 (Bolivia, 374 isolates tested) of the 11 reporting countries (Table 2). Overall, resistance to ciprofloxacin was 11% (1014/9259) and increased from 2% (19/784) of isolates tested in 2000 to 31% (311/1015) in 2009 ($P < 0.001$) (Fig. 1). Since 2005, aggregated resistance to ciprofloxacin overall remained above 6%, and significant increases in percentages of resistant isolates were observed between 2004 (4%, 37/935) and 2005 (6%, 64/1040) ($P = 0.03$) (supplementary data available at www.gasp-lac.net). Ciprofloxacin resistance increased from 1% (3/323) of *N. gonorrhoeae* isolates tested in Argentina in 2000 to 23% (71/310) in 2009 (Fig. 1). In Chile and Uruguay, ciprofloxacin resistance was first noted in 2004 with 1% (1/126) and 8% (2/25), respectively, of *N. gonorrhoeae* tested being resistant. In Chile, ciprofloxacin resistance increased significantly

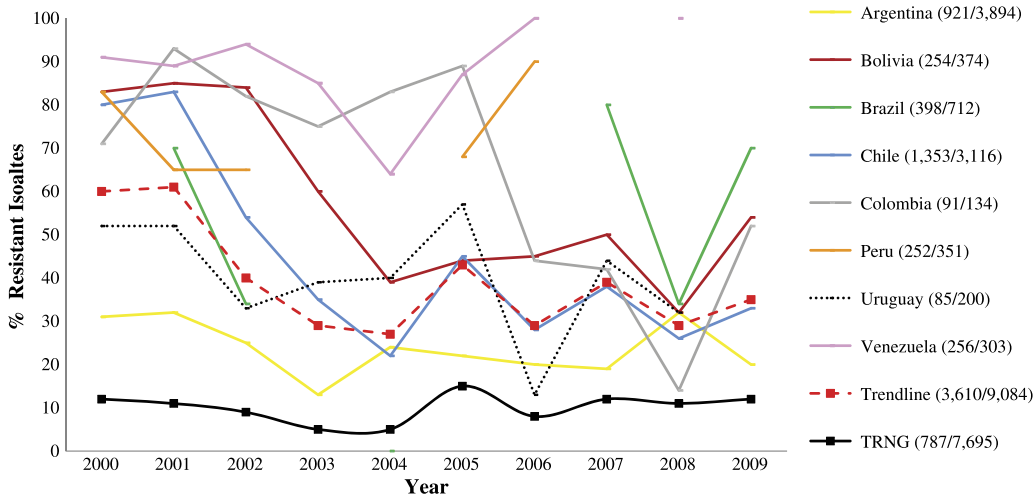

Figure 4. Trends in percentages of tetracycline resistant *N. gonorrhoeae* isolates in 8 countries in South America, 2000–2009.

TABLE 3. Treatment Guidelines for Uncomplicated Gonorrhea Recommended in South American Countries and Cuba

Antibiotics and Dose Recommended	Country	Reference for the Most Recent Guideline*
Ciprofloxacin 500 mg (s. d.)	Bolivia	Correspondence[†]
Ciprofloxacin 500 mg (s. d.) Cefixime 400 mg (s.d.)	Argentina[‡]	Ministerio de Salud, Argentina, 2004
Ciprofloxacin 500 mg (s. d.)	Brazil[‡]	Ministerio de Salud, Brazil, 2006
Ceftriaxone 250 mg (s. d.)	Paraguay[‡]	Ministerio de Salud, Paraguay, 2007
Ciprofloxacin 500 mg (s. d.)	Colombia	Ministerio de Salud, Colombia, 2000
Ceftriaxone 250 mg (s. d.) Azithromycin 1 g (s. d.)	Uruguay	Correspondence[†]
Ceftriaxone 250 mg (s. d.)	Cuba	Programa nacional de control ITS/VIH, Cuba, 2004
Cefixime 400 mg (s. d.) Spectinomycin 2 g (s. d.)	Peru[‡]	Ministerio de Salud, Peru, 2001
Ceftriaxone 250 mg (s. d.)	Chile	Ministerio de Salud, Chile, 2007

*Does not include cotreatment of *Chlamydia trachomatis.*

[†]Presentation at the GASP-LAC workshop held in Buenos Aires, Argentina, 2–4 November, 2010.

[‡]Argentina also recommends ofloxacin 400 mg (s.d.), gatifloxacin 400 mg (s.d.), levofloxacin 250 mg (s.d.) and ceftriaxone 125 mg (s.d.); Brazil also recommends ofloxacin 400 mg (s.d.), Paraguay also recommends cefixime 400 mg (s.d.) and ofloxacin 400 mg (s.d.); Peru also recommends azithromycin 1 g (s.d.) coupled with ciprofloxacin and ceftriaxone 125 mg (s.d.) instead of 250 mg (s.d.).

s.d. indicates single dose.

from 1% in 2004 to 46% (214/463) in 2009 ($P < 0.01$), whereas in Uruguay resistance percentages fluctuated in the late 2000s (Fig. 1). Colombia reported ciprofloxacin resistant isolates in 2007 (25%; 3/12) and in 2009 (24%; 6/25; Fig. 1). In Venezuela, resistance ranged from 41% (13/32) of isolates tested in 2000 to 100% (15/15) in 2007 to 47% (7/15) in 2008 (Fig. 1). Five countries tested ciprofloxacin susceptibility sporadically (Fig. 1). Resistance to ciprofloxacin was reported from Brazil in 2008 (6%; 5/77) and 2009 (2%; 2/120); 35% (14/40) from Cuba in 2009; and 8% (3/35) from Peru in 2000 and 60% (24/40) in 2006 (Fig. 1). Paraguay, reported an increase in ciprofloxacin resistance from 12% of isolates tested in 2006 to 27% in 2009. Ecuador only tested isolates in 2009 (6/7 were resistant) (supplementary data available at www.gasp-lac.net).

Azithromycin Susceptibility

Four of 6 countries reporting on trends in azithromycin susceptibility reported resistant *N. gonorrhoeae* isolates. Overall, aggregated azithromycin resistance was 13% (1088/8373), ranging from 6% (39/646) of *N. gonorrhoeae* isolates tested in 2000 to 23% (225/962) in 2009 (Fig. 2). A sharp overall increase in the percentage of azithromycin-resistant *N. gonorrhoeae* was observed between 2004 (6%, 49/847) and 2005 (10%, 105/1001) ($P < 0.001$, supplementary data available at www.gasp-lac.net). Chile reported 3% (8/244) azithromycin resistance in *N. gonorrhoeae* isolates tested in 2000 and 46% (211/463) in 2009 ($P < 0.001$). In Uruguay, resistance to azithromycin first appeared in 2001 (6%, 2/31) and increased from 6% (1/18) in 2003 to 9% (4/44) in 2009 (Fig. 2). Brazil reported resistance to azithromycin in 2004 (22%, 9/41), 2007 (6%, 7/110) and 2009 (1 isolate, Fig. 2). The percentage of azithromycin-resistant isolates in Argentina significantly decreased from 10% (31/323) in 2000 to 3% (9/310) in 2009 ($P = 0.001$) (Fig. 2). In Colombia and Peru, no azithromycin resistance was observed over the entire study period; however, Peru reported that 34% (121/351) of isolates had decreased susceptibility to azithromycin (data not shown).

Penicillin and Tetracycline Susceptibility

Overall, aggregated resistance to penicillin was 28% (3206/11,369) in 9 reporting countries (supplementary data, available at: www.gasp-lac.net) with resistance percentages being fairly steady over the 2000s [(35%, 441/1241) in 2000 and 26% (258/975) in 2009] Fig. 3. Steady percentages of penicillin resistance between 2000 and 2009 were especially noted in Argentina [24% (78/323) – 20% (63/310)], Chile [26% (64/244) – 31% (146/463)], Colombia [59% (10/17) – 56% (14/25)], Uruguay [9% (2/21) – 16% (7 PPNG/44)], and Venezuela [84% (27/32) – 87% (13/15)] Fig. 3. Resistance to penicillin increased in Bolivia, [from 38% (43/114) in 2000 to 62% (8/13) in 2009 (P = 0.3)], in Peru [from 26% (9/35) in 2000 to 80% (32/40) in 2006 (P = 0.009)] (Fig. 3) and in Paraguay (0% to 20% from 2006 to 2009, supplementary data available at: www.gasp-lac.net). Ecuador reported 6 penicillin resistant isolates of 7 *N. gonorrhoeae* isolates tested in 2009 (supplementary data available at www.gasp-lac.net). Brazil reported a significant decrease of N. Brazil reported a significant decrease of *N. gonorrhoeae* penicillin-resistant isolates from 46% (208/455) in 2000 to 17% (20/120) of isolates tested in 2009 (P < 0.001), (Fig. 3).

In the 7 countries reporting on the prevalence of β-lactamase-producing isolates (PPNG) (Table 2), the overall burden of PPNG was 21% (2322/10,844; the denominator reflects the total number of isolates tested in countries reporting PPNG). A significant decrease in PPNG isolates was observed from 31% (381/1209) of isolates tested in 2000 to 20% (175/855) in 2009 ($P < 0.001$) (Fig. 3).

The overall burden of resistance to tetracycline in 8 reporting countries was 40% (3610/9084) (Fig. 4). A significant decrease in tetracycline resistance was observed between 2000 and 2009. In 2000, 60% (476/792) of isolates tested were resistant as compared with 35% (323/931) in 2009 ($P < 0.001$) (Fig. 4). Several countries reported decreasing resistance to tetracycline on a yearly basis between 2000 and 2009 (Fig. 4), i.e., Argentina, 32% (102/323) to 20% (63/310); Bolivia, 83% (95/114) to 54% (7/13); Chile, 80% (195/244) to 33% (152/463); Colombia, 71% (12/17) to 52% (13/25); and Uruguay, 52% (14/27) to 32% (8/25). Brazil and Peru reported tetracycline antimicrobial susceptibility sporadically and showed a steady level of tetracycline resistance over the years tested, with overall percentages of 56% (398/712) and 72% (252/351) of isolates tested, respectively (supplementary data available at www.gasp-lac.net). In Venezuela, most of the isolates tested (2000–2008) were resistant to tetracycline, ranging from 91% (29/32) in 2000 to 100% of 15 isolates tested in 2008 (Fig. 4). Percentages of tetracycline resistance in Paraguay indicated an increase 40% in 2006 to 60% of isolates tested in 2009 (supplementary data available at www.gasp-lac.net).

Five of the 11 countries reported TRNG phenotypes based on MIC value (Table 2). The overall percentage of TRNG in all these countries was 10% (787/7695), with 12% (79/646) of isolates tested in 2000 being TRNG and in 2009 (96/798) (Fig. 4).

Susceptibility to Ofloxacin, Gentamicin, Erythromycin, and Chloramphenicol

Brazil reported 3% resistance to chloramphenicol in 2002 (4/115 isolates tested) and 5% (6/120) in 2009. Low levels of

resistance to gentamicin (3%, 4/122) and ofloxacin (2%, 2/120) were also reported from Brazil in 2009.

Gonorrhea Treatment Guidelines

Our retrospective analysis of current and past treatment guidelines over the period indicated that either ceftriaxone 250 mg (or 125 mg) (single dose) or ciprofloxacin 500 mg (single dose) was recommended as primary treatment for uncomplicated gonococcal infections in 7 of 9 countries providing this information. In Bolivia, ciprofloxacin 500 mg (single dose) is the first-line treatment for uncomplicated gonococcal infections. In Chile, ceftriaxone 250 mg (single dose), replacing ciprofloxacin, was adopted as primary treatment for uncomplicated gonococcal infections in 2007. Options used in other countries for the treatment of uncomplicated gonococcal infections include cefixime 400 mg (single dose; 4 countries), spectinomycin 2g (single dose, 2 countries) and azithromycin 1g (single dose, 3 countries) (Table 3).

DISCUSSION

Gonorrhea is a significant global public health burden with 88 million new cases reported worldwide each year.[36] Successful antibiotic treatment plays a key role in controlling gonococcal disease. Therefore, various initiatives have been directed at promoting and sustaining national and international gonococcal antimicrobial susceptibility surveillance as a key measure to promptly inform and update treatment guidelines for gonococcal infections.[1] The present retrospective study builds on data obtained in GASP studies during the 1990s in 11 South American and the Caribbean countries from 2000 to 2009.

Our results underscore the requirement for periodic, national, and regional treatment guideline reviews based on up-to-date AMR data for *N. gonorrhoeae*. Ciprofloxacin was discontinued as a treatment for gonococcal disease in many countries in the mid-2000s when resistance to this antibiotic became endemic.[4] This antibiotic was replaced by extended spectrum cephalosporins (ceftriaxone and cefixime).[4–6] Over the period of our retrospective analysis, ciprofloxacin was listed as one of the first-line treatment choices for gonorrhea infections in most of the participating countries, largely because resistance to this antibiotic in the region was undocumented, until recently.[37,38] The current study, which encouraged participants to retrospectively analyze raw data that had been collected during this period, shows that ciprofloxacin resistance emerged during the mid-2000s in most countries in South America and increased appreciably by the late 2000s. When resistance levels exceed 5% of isolates tested, it has been the practice to consider alternative treatment regimens and antibiotics.[38,39] Our analysis of aggregated data shows that ciprofloxacin may no longer be appropriate for treatment of gonococcal disease in most countries. However, a caveat to this conclusion would encourage broader *N. gonorrhoeae* antimicrobial susceptibility surveillance within countries so that a more representative sample could be considered. Pockets of susceptibility to ciprofloxacin have been noted internationally, and some countries continue to recommend the use of ciprofloxacin for treatment under restricted conditions, such as on-going surveillance.[40,14]

Our analysis also shows an increase in the percentage of resistant isolates to azithromycin in South America. Notably, the first report of high-level resistance to this agent originated in Argentina.[41] Therefore, treatment guidelines in the region, which include the sole use of azithromycin 1 g single dose, should be reviewed and AMR data updated. A 1 g regimen of azithromycin is not recommended for the treatment of gonorrhea as it may contribute to the rapid emergence of resistant isolates as compared with a 2 g dose.[15,16] Azithromycin 1 g (orally in single dose) combined with ceftriaxone is recommended to treat gonococcal pharyngeal infections in the United Kingdom and the United States.[15,16] In the United Kingdom, this treatment regimen is also recommended for uncomplicated gonococcal infections.[15] This underscores the importance of monitoring antimicrobial susceptibility to azithromycin as this agent is an option for combination therapy.

The majority of isolates tested in South American countries reporting during the period were susceptible to ceftriaxone. Notably, however, 7 isolates with ceftriaxone MICs >0.25 μg/ml were reported from Brazil in 2007. Although these findings were not confirmed, they underscore the need to routinely monitor antimicrobial susceptibility to extended spectrum cephalosporins, as treatment failure of pharyngeal gonococcal infections caused by strains with these MICs has been reported.[42]

Cefixime (400 mg) was recommended as an option in the treatment guidelines of 4 LAC countries during the 2000s. Nevertheless, MIC determinations to this agent are rarely conducted in the region. Despite recent reports of cefixime treatment failures in Japan[10] and Europe,[11–13] this agent still represents a valid treatment option for uncomplicated gonorrhea. For example, Canada recently recommended a higher dose of cefixime (800 mg instead of 400 mg as previously recommended),[14] whereas in the United Kingdom and the United States, cefixime is recommended in specific circumstances.[15,16] Enhanced *N. gonorrhoeae* those countries using cefixime for treatment. These countries should also be alert to possible treatment failures with this antibiotic and such isolates should be tested for AMR.

All isolates tested in this study were susceptible to spectinomycin, although 1 country (Colombia) reported decreased susceptibility to this agent. Spectinomycin is unavailable in many countries worldwide. Because *N. gonorrhoeae* isolates remain susceptible to spectinomycin, despite occasional reports of resistance when the drug is used as sole therapy, it remains a viable therapeutic option, and it is used for treatment of people with allergies to cephalosporins.[14,15,43–45]

Penicillin and tetracycline have not been recommended for the treatment of gonorrhea for several decades. In view of the limited resources for *N. gonorrhoeae* AMR testing, the continued surveillance of resistance to these agents is probably not cost effective, especially in resource-limited settings. In the present retrospective study, decreased trends in resistance to these agents were noted in the 2000s as compared with the 1990s.[24] Even so, the percentages of resistant isolates remains high, including plasmid-mediated resistance to penicillin, possibly exacerbated by the access to over the counter antibiotics and self-medication. In Brazil, the susceptibility to additional antimicrobial agents currently not used as first-line treatment for gonorrhea (i.e., chloramphenicol, ofloxacin, gentamicin, and erythromycin), was reported. Such data are especially useful for consideration of alternative treatment regimens.

Some of the limitations of the present retrospective study include wide variability in the ability of countries to undertake GASP surveillance, variability in the number of isolates and antimicrobial agents tested by each country, and also in the extent of reporting (i.e., coverage in any country, continuous or periodic testing). Interestingly, methodology used for AMR testing was quite standardized, largely due to the success of GASP-LAC Phase 1 in this regard.

The current study shows that antimicrobial susceptibility testing of *N. gonorrhoeae* isolates was on-going, at a certain level, in many countries/regions, but the data remained unanalyzed and unavailable for public health policy development (i.e., effective treatment guidelines). This underscores the importance of

a sustained infrastructure to encourage both the development of antimicrobial susceptibility information for *N. gonorrhoeae* and its timely analysis and communication. A more sustained network would assist with problem solving and perhaps study design. In the 1990s, 41 countries, including many Caribbean countries, reported at some level on *N. gonorrhoeae* antimicrobial susceptibility. Since then capacity for testing has been lost and in our study, only 11 of 41 countries contacted felt that they could participate in this retrospective study. Incremental progress is being made in contacting all countries in the region, but this effort must be sustained over a long period.[31] Furthermore, most *N. gonorrhoeae* isolates recovered over the 2000s were isolated from la limited number of large population centers. More representative, country-wide coverage for AMR surveillance is important to ascertain the representativeness of the AMR data; this tool remains an important challenge for the GASP network. Additional efforts, including integrated approaches at various regional decisional levels about linkage between national health authorities and national GASP-LAC members, are also required to support sustainable *N. gonorrhoeae* AMR surveillance in the region.

In conclusion, our study underscores the importance of ongoing antimicrobial susceptibility monitoring of *N. gonorrhoeae* to inform appropriate local/regional/country-wide treatment strategies and to ensure that first-line therapies remain effective. In doing so, this will reflect the ever-changing AMR profiles of *N. gonorrhoeae* isolates.

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