

High resistance to ciprofloxacin, tetracycline, and penicillin and emergence of decrease susceptibility to ceftriaxone in *Neisseria gonorrhoeae*, Cuba, 2009-2013

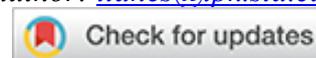
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ABSTRACT

Antimicrobial-resistant *Neisseria gonorrhoeae* remains a global public health threat, and contemporary data from the Caribbean region are scarce. We conducted a nationwide analysis of 152 isolates collected in Cuba between 2009 and 2013 to characterize antimicrobial susceptibility patterns and major chromosomal and plasmid-mediated resistance phenotypes. Susceptibility to penicillin, tetracycline, ceftriaxone, ciprofloxacin, spectinomycin, gentamicin, and azithromycin was determined using the E-test method according to CLSI criteria. High resistance to ciprofloxacin (69.7%), tetracycline (40.1%), and penicillin (36.8%) was identified, along with moderate resistance to azithromycin (13.8%). Two isolates exhibited decreased susceptibility to ceftriaxone (MIC = 0.5 µg/mL), and two others to gentamicin (MICs of 32 and 64 µg/mL); six isolates were multidrug-resistant *N. gonorrhoeae* (MDR-GC). However, no extensively drug-resistant (XDR) isolates were detected. These findings support the continued use of ceftriaxone but highlight the urgent need for enhanced surveillance, including molecular characterization, to prevent the establishment of extensively drug-resistant gonorrhoea in Cuba.

Keywords: *Neisseria gonorrhoeae*; antimicrobial resistance; Cuba; susceptibility; ceftriaxone; azithromycin; MDR-GC.

INTRODUCTION

Sexually transmitted infections (STIs) continue to be a significant global public health issue, with an annual estimated 374 million people aged 15- 49 years becoming infected with one of four curable STIs: syphilis, chlamydia, gonorrhoea, and trichomoniasis.¹ *Neisseria gonorrhoeae*, which causes gonorrhoea, is recognized as one of the pathogenic bacteria requiring urgent attention for prevention and control by the World Health Organization (WHO). Gonococci can develop resistance to various antibiotic classes, including extended-spectrum cephalosporins such as ceftriaxone, the drug of choice for gonorrhoea treatment.²

In Cuba, gonorrhoea is the second most frequently reported STI to the health authorities. However, the number of reported cases has decreased over the past 30 years, from 45.200 (411 cases per 100.000 inhabitants) in 1995 to 2.583 (26 cases per 100.000 inhabitants) in 2024. In addition, most symptomatic cases are syndromically managed.³ Cuba began the monitoring of *N. gonorrhoeae* antimicrobial surveillance data from 1995 and notified the endemic circulation of isolates with high levels of antimicrobial resistance (AMR) to penicillin and tetracycline.^{4,5}

The WHO is working to promote a global surveillance program (GASP) to establish what antimicrobials are effective for treatment of *N. gonorrhoeae* infections^{2,4}. Although sporadic investigations of *N. gonorrhoeae* antimicrobial susceptibility have been conducted in Cuba, these studies have been infrequent due to economic

constraints.^{6,7} The current study is part of the GASP program in Latin America and the Caribbean (GASP-LAC) and was developed to characterize the antimicrobial susceptibility profile and main phenotypes of chromosomal and plasmid resistance to penicillin, tetracycline, and other antibiotics of 152 *N. gonorrhoeae* isolated in Cuba between 2009 and 2013.

MATERIAL AND METHODS

Bacterial strains and identification

A total of 637 isolates presumptively identified as gonococci were recovered from genital and extragenital specimens from male and female patients across 14 out of 15 Cuban provinces between 2009 and 2013. All isolates were transported to the National Reference Laboratory of Neisseria and Helicobacter (NRLNH) in Havana using a gonococcal transport medium developed in Cuba (patent CU22547A1).

Of the 637 recovered isolates, 152 (121 from male patients and 31 from female patients) were confirmed as *N. gonorrhoeae* at the NRLNH based on growth on Thayer–Martin selective agar, Gram-negative diplococci morphology, positive oxidase and catalase (30% hydrogen peroxide) tests, and carbohydrate utilization patterns.⁴ Confirmed isolates were subcultured onto chocolate GC medium base agar (Liofilchem, Italy) supplemented with 1% Vitox (Oxoid, USA) (GCMV medium agar) and screened for β -lactamase production using nitrocefin (Oxoid, USA). Isolates were stored at $-70\text{ }^{\circ}\text{C}$ in trypticase soy broth supplemented with 20% glycerol until testing.

Antimicrobial susceptibility testing

Frozen isolates were thawed and subcultured onto chocolate agar for 24 h at $35\text{--}37\text{ }^{\circ}\text{C}$ in 5% CO_2 . A bacterial suspension was prepared and adjusted to a 0.5 McFarland standard for inoculation onto GCMV medium agar plates. Minimum inhibitory concentrations (MICs) were determined using Etest® strips (AB Biodisk, Sweden; Liofilchem, Italy) in accordance with CLSI M100 document for the majority of antibiotic⁸ and Mann et al⁹ for gentamicin.

The antimicrobials tested were:

Penicillin G, tetracycline, ceftriaxone, ciprofloxacin, spectinomycin, gentamicin, and azithromycin.

Quality control strains included *N. gonorrhoeae* WHO M, WHO G, WHO P, and ATCC 49226, tested with each batch.

MICs were read after 24 h of incubation at $35\text{ }^{\circ}\text{C}$ in 5% CO_2 (Incubator Hirayama, Japan).

Interpretive criteria

Breakpoints for susceptibility (S), intermediate (I), and resistance (R) followed CLSI M100 $\mu\text{g/mL}$):

- Penicillin: $S \leq 0.06$; $I = 0.12\text{--}1$; $R \geq 2^8$
- Tetracycline: $S \leq 0.25$; $I = 0.5\text{--}1$; $R \geq 2^8$
- Spectinomycin: $S \leq 32$; $I = 64$; $R \geq 128^8$
- Ciprofloxacin: $S \leq 0.06$; $I = 0.12\text{--}0.5$; $R \geq 1^8$
- Azithromycin: $S \leq 1^8$
- Ceftriaxone: $S \leq 0.25^8$
- Gentamicin: $S \leq 4$; $I = 8\text{--}16$; $R \geq 32^9$

As CLSI recommendations have only defined susceptibility criteria of *N. gonorrhoeae* for ceftriaxone and azithromycin ($\text{MIC} \leq 0.25\text{ g/L}$ and $\leq 1\text{ g/L}$), respectively, we used European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) recommendations to define resistance to ceftriaxone ($\text{MIC} \geq 0.5\text{ }\mu\text{g/mL}$) and azithromycin ($\text{MIC} > 1\text{ }\mu\text{g/mL}$).¹⁰

Definition of resistance phenotypes

Phenotypic classifications for *N. gonorrhoeae* antibiotic resistance followed established criteria:

Plasmid-mediated resistant phenotypes

- PPNG: penicillinase (β -lactamase)-positive isolates
- TRNG: tetracycline resistance with MIC values $\geq 16 \mu\text{g/mL}$
- PP/TRNG: β -lactamase-positive isolates and tetracycline resistance with MIC values $\geq 16 \mu\text{g/mL}$

Chromosomally mediated resistance

- CMTR: tetracycline resistance with MIC values $\geq 2 \mu\text{g/mL}$ (in the absence of TRNG or PP/TRNG)
- CMPR: penicillin resistance MIC values $\geq 2 \mu\text{g/mL}$ (in the absence of PPNG)
- CMRNG: dual chromosomal resistance to both penicillin and tetracycline (MIC $\geq 2 \mu\text{g/mL}$)

Chromosomal resistance to ciprofloxacin (MIC $\geq 1 \mu\text{g/mL}$), gentamicin (MIC $\geq 32 \mu\text{g/mL}$),⁺ and to spectinomycin (MIC $\geq 128 \mu\text{g/mL}$) was also recorded.^{7,10}

Classification of multidrug-resistant and extensively drug-resistant *N. gonorrhoeae* isolates

Definitions followed international consensus guidelines.^{10,11}

- Multidrug-resistant gonococci (MDR-GC):
Decreased susceptibility or resistance to one currently recommended therapy (ceftriaxone or azithromycin) PLUS resistance to at least two additional antimicrobial classes (penicillin, tetracycline, azithromycin, ciprofloxacin, gentamicin, or spectinomycin).
- Extensively drug-resistant gonococci (XDR-GC):
Decreased susceptibility or resistance to both currently recommended therapies (ceftriaxone and azithromycin) PLUS resistance to at least two additional antimicrobial classes.

RESULTS

A total of 152 *N. gonorrhoeae* isolates were recovered from symptomatic patients across 14 Cuban patients between 2009 and 2013. All isolates were confirmed using standard biochemical and microscopic procedures before susceptibility testing.

Geographic distribution of isolates

Gonococcal isolates were obtained from 14 out of 15 Cuban provinces and the special municipality of Isla de la Juventud (MEIJ, acronym in Spanish), which participates in the national surveillance program, except Ciego de Ávila. Distribution of isolates by geographical regions: Western (43), Centre (18), and Eastern (91), ensuring broad geographic coverage.

Distribution of isolates by provinces was: Pinar del Rio (1), Artemisa (15), Mayabeque (6), La Habana (19), Matanzas (16), Cienfuegos (3), Villa Clara (9), Sancti Spiritus (2), Camagüey (4), Las Tunas (2), Holguin (10), Granma (5), Santiago de Cuba (33), Guantanamo (25) and MEIJ (2), ensuring broad geographic coverage.

Although province-specific resistance data were unavailable, the distribution of sampling sites and detected resistance phenotypes by geographical regions is shown below

Long-term resistance trends (1995–2013)

Historical AMR data (1995–2008) were incorporated to contextualize the findings. Ciprofloxacin resistance increased steadily, reaching 69.7% in 2009–2013. Tetracycline and penicillin resistance declined relative to earlier surveillance periods, but remained high (Figure 1).

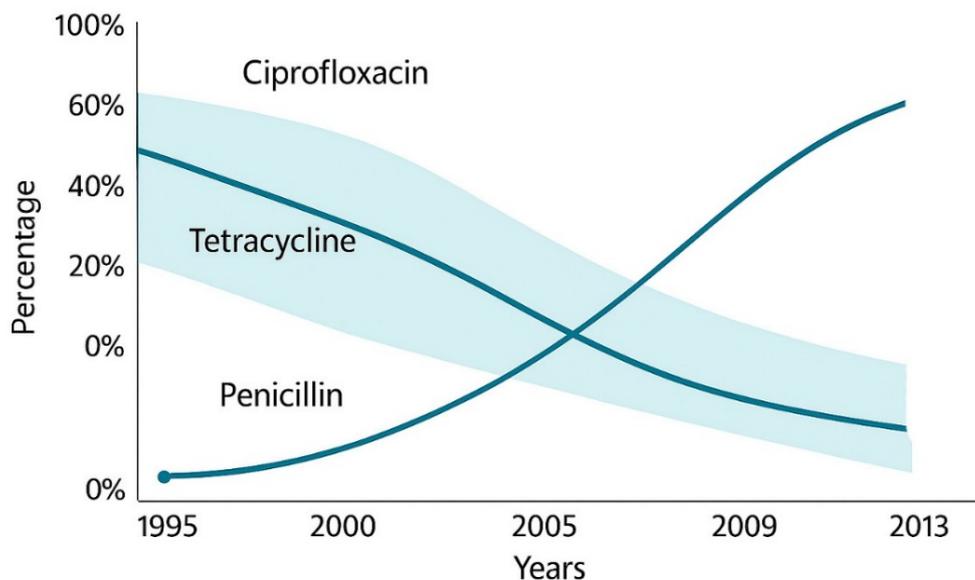


Figure 1. Temporal trends in antimicrobial resistance of *N. gonorrhoeae* in Cuba, 1995–2013. Data from 1995–2008 were reconstructed from previously published studies.^{4,7,12}

Overall antimicrobial susceptibility

Ciprofloxacin exhibited the highest resistance level (69.7%).

Tetracycline and penicillin resistance were 40.1% and 36.8%, respectively, while 52.6% of isolates showed intermediate susceptibility to penicillin.

Azithromycin resistance was 13.8%

Most isolates remained susceptible to spectinomycin (99.3%) and gentamicin (79.6%); however, two isolates showed decreased susceptibility to ceftriaxone (MIC = 0.5 µg/mL).

Antibiotic	S n (%)	I n (%)	R n (%)	MIC range (µg/mL)
Penicillin	16 (10.5%)	80 (52.6%)	56 (36.8%)	0.004–64
Tetracycline	25 (16.5%)	66 (43.2%)	61 (40.1%)	0.016–256
Ciprofloxacin	25 (16.5%)	21 (13.8%)	106 (69.7%)	0.002–64
Spectinomycin	151 (99.3%)	1 (0.7%)	0	4–64
Ceftriaxone	150 (98.7%)	2 (1.3%)	0	0.001–0.5
Azithromycin	77 (50.7%)	54 (35.5%)	21 (13.8%)	0.016–256
Gentamicin	121 (79.6%)	29 (19.1%)	2 (1.3%)	0.5–64

Number (n) Susceptible (S), intermediate (I), and resistant (R) categories were determined using CLSI M100 interpretive criteria. MIC ranges are expressed in µg/mL.

Table 1. Antimicrobial susceptibility of 152 *Neisseria gonorrhoeae* isolates in Cuba, 2009–2013.

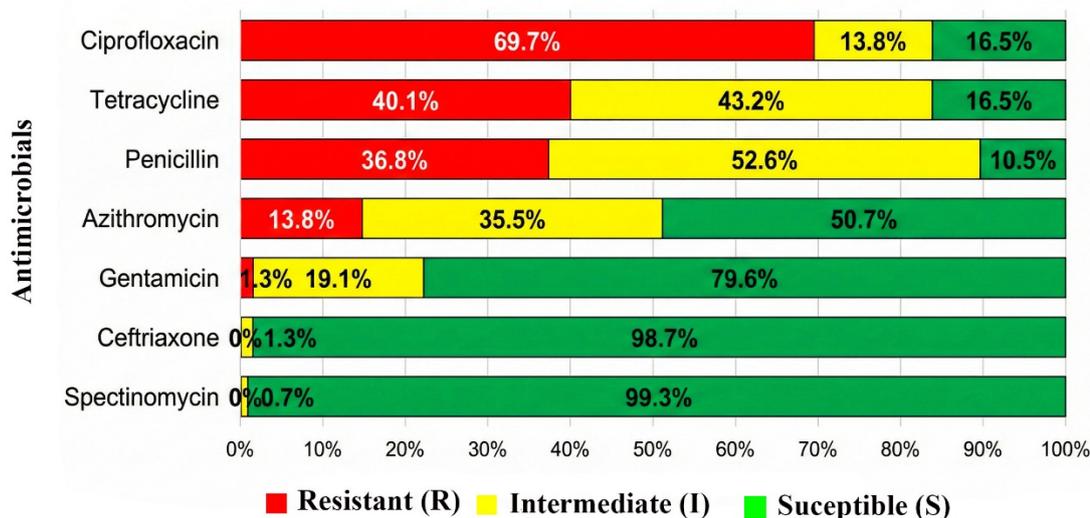


Figure 2. Proportion of 152 *Neisseria gonorrhoeae* isolates from Cuba (2009–2013) classified as susceptible, intermediate, or resistant to other antimicrobials (ceftriaxone, spectinomycin, and gentamicin) were excluded for analysis because percentages of intermediate susceptibility or resistance were $\leq 2 \mu\text{g/mL}$.

Resistance phenotypes

Both plasmid-mediated and chromosomally mediated phenotypes of resistance were identified:

The distribution of resistant phenotypes among *N. gonorrhoeae* isolates by geographical region is shown in Table 2.

Quinolone-resistant *N. gonorrhoeae* (QRNG) phenotype, alongside with those showing plasmidic resistance to penicillin, tetracycline, or both antibiotics (PPNG, TRNG, PP/TRNG), and isolates having combined chromosomally-mediated resistance to penicillin and tetracycline (CMRNG), were distributed in all three Cuban regions. However, CMPR resistance phenotypes predominated in gonococci isolates from the western region, and CMTR phenotypes were more frequently identified from the western and eastern areas.

The majority of PP/TRNG isolates (14/16) were recovered during the years 2011-2013, and the CMTR isolate was detected in isolates from all years, except 2009.

Both *N. gonorrhoeae* isolates displaying decreased susceptibility to ceftriaxone were obtained during 2009 in Havana province (western region).

Geographical region	QRNG	PP/TRNG	PPNG	TRNG	CMPR	CMTR	CMRNG	AZRNG	DS-CEFT
Western	38	7	7	5	7	7	2	9	2
Centre	10	2	2	3	0	1	3	6	0
Eastern	58	16	7	6	2	8	1	6	0
Total	106	25	16	14	9	16	6	21	2

PPNG=penicillinase-producing *N. gonorrhoeae*; TRNG=tetracycline-resistant *N. gonorrhoeae* (plasmidic); PP/TRNG=PPNG+TRNG; CMTR=chromosomally mediated tetracycline resistance; CMPR=chromosomally mediated penicillin resistance; CMRNG=chromosomally mediated resistance to both penicillin and tetracycline; AZRNG=azithromycin-resistant *N. gonorrhoeae* and DS-CEFT=decreased susceptibility to ceftriaxone. QRNG=quinolone-resistant *N. gonorrhoeae*

Table 2. Distribution of resistance phenotypes of resistance phenotypes of 152 *Neisseria gonorrhoeae* isolates by geographical regions, Cuba, 2009-2013

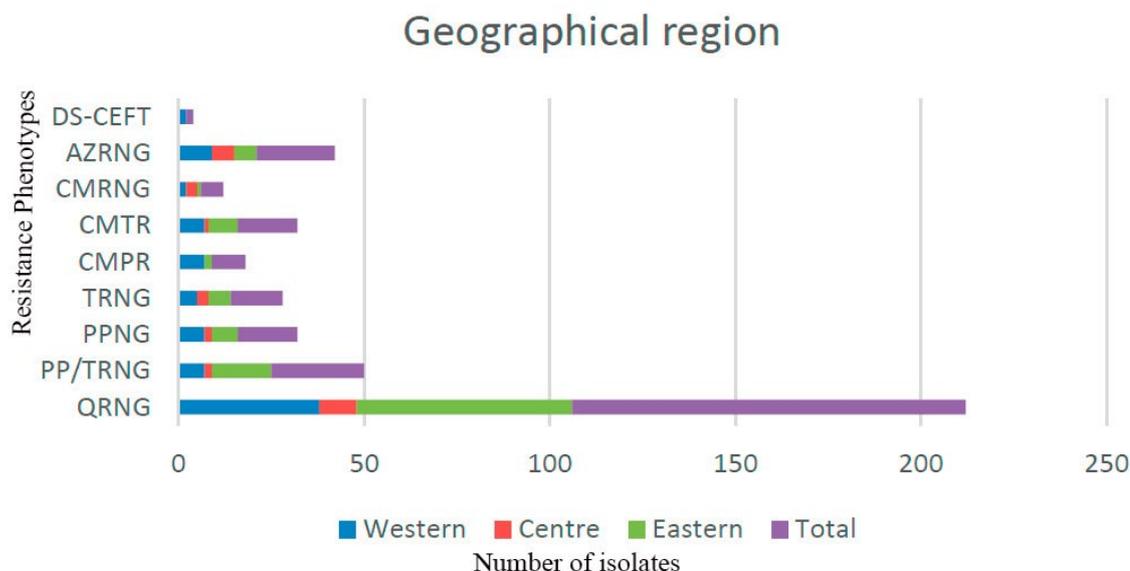


Figure 3. Distribution of antimicrobial resistance phenotypes among *Neisseria gonorrhoeae* isolates from Western, Central, and Eastern Cuba (2009–2013). Bars represent the absolute number of isolates exhibiting each phenotype: QRNG (quinolone-resistant *N. gonorrhoeae*), PP/TRNG (combined penicillinase- and tetracycline-resistant), PPNG (penicillinase-producing), TRNG (tetracycline-resistant), CMPR (chromosomally mediated penicillin resistance), CMTR (chromosomally mediated tetracycline resistance), CMRNG (combined chromosomal resistance to penicillin and tetracycline), AZRNG (azithromycin-resistant), and DS-CEFT (decreased susceptibility to ceftriaxone).

Multidrug-resistant gonococci (MDR-GC)

Six isolates (3.9%) met MDR-GC criteria. Three had azithromycin resistance (AZRNG) in combination with plasmid-mediated resistance to penicillin and tetracycline (PP/TRNG), and also QRNG resistance. Two other AZRNG isolates were also QRNG and PPNG, and the remaining AZNGR isolate exhibited combined resistance to other three antimicrobials, penicillin, tetracycline, and ciprofloxacin (CMPR, TRNG, and QRNG). No extensively drug-resistant isolates (XDR-GC) were detected.

MIC distribution for ceftriaxone and azithromycin

The MIC for 90% of gonococci isolates (MIC₉₀) to ceftriaxone was 0.032 µg/mL; however, two isolates had MICs of 0.5 µg/mL, indicating decreased susceptibility to this antibiotic.

Azithromycin MIC values ranged from 0.016 to 256 µg/mL, and the MIC₉₀ was 0,25 µg/mL. Seven of 21 resistant isolates showed high-level of resistance to this macrolide (HL-AziR) (MIC_≥256 µg/mL), representing 3.94% of total isolates.

DISCUSSION

Between 2009 and 2013, *Neisseria gonorrhoeae* isolates collected across Cuba exhibited consistently high levels of AMR, particularly to ciprofloxacin (69.7%), tetracycline (40.1%), and penicillin (36.8%). These findings extend and update previous national surveillance reports that documented high levels of resistance to penicillin and tetracycline in the late 1990s.⁴⁻⁷ Ciprofloxacin was introduced as first-line treatment for gonorrhoea in Cuba in 2002 due to its excellent in vitro activity,⁴ yet resistance subsequently emerged in the early 2000s⁶ and continued to increase, consistent with patterns observed in several regions participating in GASP-LAC.¹² Our data confirm that this trend persisted, aligning with international reports indicating a marked increase in fluoroquinolone resistance across Latin America and the Caribbean (LAC).^{12,13} A recent

global meta-analysis further contextualizes these observations, reporting a weighted pooled resistance to ciprofloxacin of 51.6% with substantial geographic variation (Asia 83%, Europe 46%, Oceania 24%).¹⁴ Penicillin resistance in our dataset (36.8%) was markedly lower than earlier Cuban reports (60.8–68%).^{4,7} Similar rates of penicillin susceptibility restoration have been documented in several countries, including Canada¹⁵ and Spain¹¹, although some regions continue to report higher resistance levels, as seen in Argentina¹⁵ and Madagascar.¹⁶ Importantly, over half of our isolates (52.6%) exhibited intermediate susceptibility to penicillin, a pattern also described in studies from Russia, where intermediate MICs (47.6%) were linked to chromosomal mutations in *penA*, *ponA*, *porA*, and *mtrR*.¹⁷ Such intermediary phenotypes remain epidemiologically relevant because they may evolve toward higher levels of resistance.

Tetracycline resistance also decreased compared with 1995–1998 (83.5%).⁷ This reduction parallels regional dynamics reported through GASP-LAC from 2000 to 2009¹². It aligns with global observations indicating a transition from plasmid-mediated resistance (PPNG, TRNG, PP/TRNG) toward chromosomally mediated mechanisms.¹⁸ In our study, plasmid-mediated resistance phenotypes declined to 16.6%, representing a notable epidemiological shift compared with more than 70% reported in earlier Cuban investigations.^{4,7}

Spectinomycin remained highly active against *N. gonorrhoeae* isolates (99.3%), consistent with global reports of sustained susceptibility.^{14,19} Its limited use is typically attributable to factors in clinical practice rather than to microbiological performance.¹⁸ Gentamicin, evaluated for the first time in Cuban gonococcal isolates, also demonstrated favourable in vitro activity, except for two resistant isolates (MICs of 32 and 64 µg/mL). A higher proportion of resistance has been reported in Nigeria and Kenya.¹⁴ Our results of intermediate susceptibility to this aminoglycoside align with the study of Le Van et al.²⁰ Although gentamicin has been considered a potential alternative in some clinical settings, several studies—including the GToG randomized trial—have shown variable efficacy depending on the anatomical site of infection.⁹

Azithromycin resistance in our dataset (13.8%) exceeds the WHO 5% threshold for empirical treatment of this STI.¹⁴ This value is higher than previously reported in Cuba (9.9%)⁷ and is comparable to increases observed across Europe, North America, Africa, and Asia.^{11,15,16,22} This is the first report in Cuba about HL-AziR isolates. In Europe, in 2023, these strains were reported by 15 countries, compared to five countries in 2022.¹¹ The global rise in macrolide resistance is multifactorial and underscores the importance of continued susceptibility monitoring, especially in contexts where azithromycin is used in dual therapy of gonococcal infections and for syndrome management of STIs,²³ as in Cuba. An important finding from this study is the identification, for the first time in Cuba, of isolates with decreased susceptibility to ceftriaxone (MIC = 0.5 µg/mL). Similar observations have been reported in France, Spain, and Argentina.^{10,11,13} These Cuban displayed co-resistance to penicillin and tetracycline but remained susceptible to azithromycin, reflecting a resistance profile compatible with early-stage ceftriaxone MIC elevation described in various countries.^{15,16} These findings are relevant in the global context of “MIC creep,” where gradual increases in cephalosporin MICs have preceded sporadic treatment failures and the emergence of mosaic *penA* alleles.^{15,16}

Another novel contribution of this study is the detection of six multidrug-resistant isolates (MDR-GC). These MDR-GC strains have been increasingly reported across different regions of the world^{10,11,24}, highlighting the need for surveillance to ensure continued treatment efficacy. Notably, no extensively drug-resistant gonococci (XDR-GC) were identified.

From a regional perspective, the AMR patterns observed in Cuba are broadly consistent with values reported across Latin America in the last two decades, particularly for fluoroquinolones and older antimicrobials.^{12,25} The present study, which includes isolates from almost all Cuban provinces, provides one of the most geographically comprehensive assessments of gonococcal AMR reported for this country and represents a valuable contribution to regional and global surveillance initiatives.

Limitations of the study

This study has several limitations.

First, the number of viable isolates available for analysis may not fully capture the diversity of circulating strains.

Second, molecular characterization methods (e.g., *penA* sequencing, *mtrR* promoter analysis, NG-MAST, whole-genome sequencing) were not performed, limiting the ability to correlate phenotypes with specific

genetic determinants.

Third, detailed epidemiological metadata (clinical presentation, behavioural factors, HIV status, prior treatments, reinfection patterns) were not available, preventing linkage between resistance patterns and transmission dynamics.

Finally, as with many surveillance-based studies, the dataset reflects isolates submitted for laboratory confirmation and may not fully represent all infections occurring in the population.

Despite these considerations, the study provides the most current, geographically broad, and phenotypically detailed dataset on gonococcal AMR in Cuba. It supports the continued value of laboratory surveillance and the progressive integration of molecular tools into future national monitoring efforts.

CONCLUSIONS

This nationwide analysis provides an updated overview of gonococcal antimicrobial resistance (AMR) in Cuba between 2009 and 2013, confirming a high burden of resistance to ciprofloxacin, tetracycline, and penicillin, and documenting, for the first time, the presence of isolates with decreased susceptibility to ceftriaxone. Although such isolates were infrequent, their detection highlights the importance of continued monitoring of cephalosporin MICs.

The identification of multidrug-resistant gonococci (MDR-GC) and the observed increase in azithromycin and the emergence of isolates with HL-AziR emphasize the need for regular evaluation of therapeutic strategies. At the same time, the absence of extensively drug-resistant (XDR) strains is reassuring and underscores the value of sustained vigilance to preserve the current effectiveness of treatment.

Overall, these findings support the ongoing use of ceftriaxone as the principal treatment option for gonorrhoea in Cuba, while indicating that periodic review of macrolide susceptibility remains advisable. Continued surveillance based on culture, MIC determination, and, where feasible, incorporation of molecular approaches will contribute to early detection of emerging resistance patterns. It will strengthen evidence-based decision-making in national gonorrhoea management.

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Conflict of Interest Statement

The authors declare no conflict of interest. The funders—including institutional entities that provided logistical support—had no role in the design of the study, the collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to publish the results.

Author Contributions

Conceptualization, R.M.; Methodology, R.M. and G.R.T.; Investigation, R.M. and H.F.A.-G.; Formal Analysis, R.M. and G.R.T.; Data Curation, R.M.; Visualization, R.M.; Writing—Original Draft, R.M.; Writing—Review and Editing, R.M., H.F.A.-G., and G.R.T.; Supervision, R.M.; Project Administration, R.M.

All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The datasets generated and analysed during this study are available from the corresponding author upon reasonable request.

Institutional Review Board Statement

Not applicable. This study did not involve human participants or animal experimentation.

Informed Consent Statement

Not applicable. No human subjects were involved in this study.

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AI-Assisted Tools Disclosure

No AI system generated, manipulated, or analysed any scientific data presented in this study. All laboratory results, susceptibility testing, and epidemiological analyses were performed entirely by the authors using validated scientific procedures.

Generative artificial intelligence tools were used exclusively for minor linguistic refinement and formatting standardization of the manuscript, under full human supervision. No AI tool contributed to scientific interpretation, data generation, or the creation of original content. The authors independently verified all results, analyses, and conclusions in accordance with BioNatura Journal's policy on AI-assisted content (<https://bionaturajournal.com/artificial-intelligence--ai-.html>).

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