Gentamicin Susceptibility in *Neisseria gonorrhoeae* and Treatment Outcomes for Urogenital Gonorrhea After 25 Years of Sustained Gentamicin Use in Malawi

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Background: Gentamicin has been used for the treatment of gonorrhea in Malawi since 1993. However, declining clinical cure rates have been suspected. We evaluated current *Neisseria gonorrhoeae* susceptibility to gentamicin in vitro and clinically.

Methods: Men with acute urethritis were recruited at the Bwaila District Hospital STI Clinic in Lilongwe, Malawi, between January 2017 and August 2019. All men provided urethral swabs for etiological testing at enrollment and test of cure (TOC), 1 week later, using Gram-stained microscopy and culture. We used Etest to determine minimum inhibitory concentrations (MICs) of gentamicin, azithromycin, cefixime, ceftriaxone, ciprofloxacin, and spectinomycin; disc diffusion for tetracycline susceptibility; and whole-genome sequencing (WGS) to verify/refute treatment failure.

Results: Among 183 *N. gonorrhoeae* culture-positive men enrolled, 151 (82.5%) had a swab taken for TOC. Of these 151 men, 16 (10.6%) had a positive culture at TOC. One hundred forty-one baseline isolates were tested for gentamicin susceptibility using Etest: 2 (1.4%), MIC = 2 μg/mL; 111 (78.7%), MIC = 4 μg/mL; and 28 (19.9%), MIC = 8 μg/mL. All isolates were susceptible to azithromycin, cefixime, ceftriaxone, and spectinomycin, whereas 63.1% had intermediate susceptibility or resistance to ciprofloxacin. Almost all (96.1%) isolates were resistant to tetracycline. All examined isolates cultured at TOC (n = 13) had gentamicin MICs ≤8 μg/mL. Ten men had pretreatment and posttreatment isolates examined by whole-genome sequencing; 2 (20%) were verified new infections (4119 and 1272 single-nucleotide polymorphisms), whereas 8 (80%) were confirmed treatment failures (0–1 single-nucleotide polymorphism).

Conclusions: Gentamicin MICs poorly predict gonorrhea treatment outcome with gentamicin, and treatment failures are verified with gonococcal strains with in vitro susceptibility to gentamicin. The first-line treatment of gonorrhea in Malawi should be reassessed.

Gonorrhea and the etiological agent *Neisseria gonorrhoeae* are important public health concerns globally, with the highest incidence in sub-Saharan Africa.[1,2] Furthermore, their public health impact has been amplified by high rates of resistance to traditional antimicrobial agents such as sulfonamides, penicillins, macrolides, tetracyclines, spectinomycin, and fluoroquinolones.[3] The high resistance rates led to the classification of drug-resistant *N. gonorrhoeae* as an "urgent threat" or "high priority" by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), respectively.[4–6] Injectable ceftriaxone, an extended-spectrum cephalosporin (ESC), in high dose as monotherapy or given in combination with azithromycin, is the current first-line treatment of uncomplicated gonorrhea in many countries per the US CDC, European, and WHO guidelines.[7–9] However, recent global data show resistance or decreased susceptibility of *N. gonorrhoeae* to ESCs and azithromycin and emergence of multidrug and extensively drug-resistant *N. gonorrhoeae* strains across several geographical settings.[10–12]

US CDC and European guidelines recommend gentamicin for alternative treatment of drug-resistant *N. gonorrhoeae* and for people with cephalosporin allergy.[7,8,13,14] However, the WHO does not recommend gentamicin in the recently revised guidelines for the management of syndromic sexually transmitted infections.[9] The gentamicin clinical and microbiological cure rates for *N. gonorrhoeae* vary widely across settings, ranging from 62% to 98%[15]; however, *in vitro* resistance to gentamicin seems rare worldwide.[16–21] Unlike most countries, Malawi has continued to use gentamicin since 1993, in combination with doxycycline and metronidazole, as first-line treatment in the syndromic management of urethritis/urethral discharge.[17,22] Antimicrobial resistance (AMR) surveillance studies in Malawi have consistently shown high clinical cure rates (90%–95%) and in vitro susceptibility of

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N. gonorrhoeae to gentamicin in men with urethritis.[17,18,23] However, a recent study from the United Kingdom showed suboptimal performance of gentamicin 240 mg in combination with azithromycin 1 g, particularly against extragenital *N. gonorrhoeae* infection (pharyngeal and rectal sites),[15] whereas another study from the Czech Republic showed a 100% clearance rate with gentamicin 240 mg and azithromycin 2 g in extragenital sites.[13]

Monitoring of the antimicrobial susceptibility of *N. gonorrhoeae* is essential in an environment of rapidly changing resistance patterns.[3,6,9–12] In Malawi, very few *N. gonorrhoeae* AMR surveillance studies have been conducted, with the last being in 2007.[18] Although gentamicin has remained the preferred choice of *N. gonorrhoeae* treatment in Malawi, declining clinical cure rates have been suspected.[24] Furthermore, surveillance of gentamicin susceptibility in *N. gonorrhoeae* in general has been affected by the lack of clinical resistance breakpoints for minimum inhibitory concentrations (MICs) of gentamicin[17,25] and differences in the MIC measured by Etest compared with agar dilution method.[26]

In this study, we conducted AMR surveillance to evaluate current *N. gonorrhoeae* in vitro and clinical susceptibility to gentamicin in Malawi using Etest and test of cure (TOC). Whole-genome sequencing (WGS) was performed to verify/refute clinical failures.

MATERIALS AND METHODS

Men with acute urethritis were recruited for study participation at the Bwaila District Hospital STI Clinic in Lilongwe, Malawi. Participants were originally recruited as part of a parent study of men living with HIV who had acute urethritis[27]; after enrollment for that study closed, an additional cohort of consecutive men with acute urethritis was recruited to increase sample size, regardless of HIV status. All participants, in both cohorts, were at least 18 years of age; lived in Lilongwe District; and provided written informed consent before study participation. All participants received a genital examination, provided urethral swabs for Gram-stained microscopy and culture, and completed a demographic and sexual behavioral survey. Participants were treated syndromically per Malawian standard of care, with gentamicin 240 mg IM STAT, doxycycline 100 mg BID for 7 days, and metronidazole 2 g single dose.[22] After treatment, all participants were provided with condoms and sexual contact cards to promote partner treatment, and were counseled to abstain from sex until after their 1-week TOC follow-up appointment. At the 1-week follow-up visit, a brief sexual behavior survey was administered, a genital examination was performed, and a urethral swab was collected from all men including those whose discharge had resolved, for TOC using Gram-stained microscopy and culture. To minimize potential misclassification from reinfection, week 1 follow-up visits had to occur within 14 days of study enrollment and treatment to be considered completed. Participants with *N. gonorrhoeae* cultured at enrollment and TOC visits were regarded as suspected treatment failures.

All urethral swabs from both visits were tested locally for *N. gonorrhoeae* infection with Gram-stained microscopy and culture. Urethral swabs were directly inoculated onto selective Thayer Martin agar media (gonococcal agar base, bovine hemoglobin, IsoVitaleX, vancomycin, colistin, nystatin) for recovery of gonococcal isolates. Cultures were incubated at 35°C in a 5% CO_2-enriched humid atmosphere and inspected for growth indicative of *N. gonorrhoeae* after 24, 48, and 72 hours. Oxidase positive colonies with morphology consistent with *N. gonorrhoeae* were species confirmed by Gram-stained microscopy and subcultured onto nonselective chocolate agar media (gonococcal agar base, bovine hemoglobin, IsoVitaleX). Disc diffusion was used for tetracycline susceptibility, in accordance with the US Clinical and Laboratory Standards Institute (www.clsi.org). All *N. gonorrhoeae* isolates cultured at enrollment and TOC visit were frozen at −80°C and shipped to the WHO Collaborating Centre for Gonorrhoea and Other STIs in Örebro, Sweden, for confirmatory AMR testing and WGS.

At the WHO Collaborating Centre for Gonorrhoea and Other STIs, viable isolates from both enrollment and TOC were tested using Etest to determine MICs of gentamicin, azithromycin, cefixime, ceftriaxone, ciprofloxacin, and spectinomycin, in accordance with the manufacturer's instructions (bioMérieux, Marcy-l'Etoile, France). Genomic DNA was extracted using the QIASymphony DSP virus/pathogen kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions. Whole-genome sequencing was performed on all isolates using Illumina Miseq sequencing platform (Illumina, Inc., San Diego, CA), in accordance with the instructions of the manufacturer. All reads were mapped to *N. gonorrhoeae* reference strain FA1090 (GenBank: AE004969.1) to obtain a multiple sequence alignment as previously described.[28] Pairwise distance was calculated using MEGA-X (https://www.megasoftware.net). For participants with *N. gonorrhoeae* cultured also at TOC after week 1, WGS sequences of pretreatment and posttreatment isolates were compared by single-nucleotide polymorphism (SNP) analysis to verify/refute suspected treatment failures, as recommended by the WHO and European Centre for Disease Prevention and Control.

We used descriptive statistics to assess AMR among *N. gonorrhoeae* isolates and clinical cure among study participants at TOC. All participants with viable *N. gonorrhoeae* isolates at the WHO Collaborating Centre were included in the primary analysis. Only participants with matched pretreatment and posttreatment isolates were included in the WGS analysis. All descriptive analyses were performed using SAS v9.4 (Cary, NC). Data collection for this study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill and the Malawian National Health Science Research Committee.

RESULTS

Enrollment and Culture Results

Between January 2017 and August 2019, 183 men with culture-positive *N. gonorrhoeae* infection were enrolled in the study (Fig. 1). The median age was 28 years (interquartile range [IQR], 25–35 years), and approximately half (51.9%) were married (Table 1). The majority (75.9%) of participants had a primary education or less and were working full-time (63.4%). Because of recruitment strategies, about 1 in 4 was living with HIV (28.4%). Participants reported a median of 5 (IQR, 2–12) sex acts and 1 (IQR, 1–2) sex partner in the last month. About half reported that their last sex partner was a main partner (53.0%), and only 10.9% reported condom use the last time they had sex (Table 1).

Among the 183 participants, 161 returned for an eligible week 1 follow-up visit (88.0%) and 151 (82.5%) had a swab collected and cultured for TOC using culture (Fig. 1). We did not have week 1 culture results for 10 participants because urethral swabs were not collected. The median time between enrollment and the week 1 follow-up visit was 7 days (IQR, 7–7 days) but ranged between 4 and 14 days. Among the 151 participants with TOC, 16 (10.6%) had a positive culture for *N. gonorrhoeae* at TOC, 8 (5.3%) of whom also had urethral discharge during the genital examination. Of these 16 participants with suspected treatment failure, 1 reported having had sex since diagnosis and treatment, and of the 12 (75%) asked, 5 reported at their follow-up visit that they had not taken all their doxycycline pills. Of the 8 who had a positive culture and observed urethritis at the week 1 follow-up visit, the majority of those asked (5 of 6 [83.3%]) reported that their urethritis had resolved at 1 point since treatment.

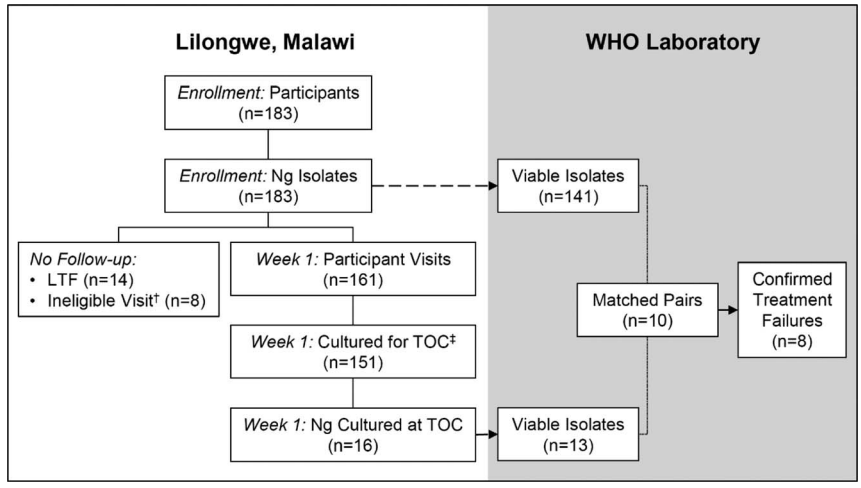

Figure 1. Collection of *Neisseria gonorrhoeae* isolates from participant visits.

Antimicrobial Resistance

Among the 183 *N. gonorrhoeae* baseline isolates, 141 were viable isolates at the WHO Collaborating Centre and were tested for gentamicin susceptibility. The majority of isolates (n = 111; 78.7%) had Etest MIC of 4 μg/mL at baseline. Two isolates (1.4%) had an MIC of 2 μg/mL, and the remaining 28 (19.9%) had an MIC of 8 μg/mL (Table 2). All isolates (100.0%) were susceptible to azithromycin, cefixime, ceftriaxone, and spectinomycin. About a third (36.9%) of the isolates were susceptible to ciprofloxacin, 21.3% showed an intermediate susceptibility, and the remaining 41.8% were resistant. Almost all (96.1%) of the isolates were resistant to tetracycline (Supplemental Table 1, http://links.lww.com/OLQ/A775).

Among the 16 *N. gonorrhoeae* isolates at the TOC visit, 13 isolates were viable at the WHO Collaborating Centre and tested for gentamicin susceptibility; 1 (7.7%) had an MIC of 2 μg/mL, 8 (61.5%) had an MIC of 4 μg/mL, and 4 (30.7%) had an MIC of 8 μg/mL (Tables 2, 3).

TABLE 1. Characteristics of Men With Positive Culture for *Neisseria gonorrhoeae* at Enrollment

Characteristic	n (%)
Total	183
Age*, y	28 (25–35)
Marital status	
Never married	56 (30.6)
Married	95 (51.9)
Separated/divorced/widowed	32 (17.5)
Education	
Some primary or less	57 (31.1)
Completed primary	82 (44.8)
Completed secondary	33 (18.0)
Any postsecondary education	11 (6.0)
Employment	
Employed full-time	116 (63.4)
Employed part-time	32 (17.5)
Unemployed	35 (19.1)
Living with HIV	52 (28.4)
No. sex acts per month*	5 (2–12)
No. partners in the past month*	1 (1–2)
Last sex with main partner	97 (53.0)
Last sex with condom	20 (10.9)

*Median (IQR).

Suspected Treatment Failures

In total, 10 participants with positive *N. gonorrhoeae* TOC cultures at the week 1 follow-up visit had both the pretreatment and posttreatment isolates viable for examination by Etest and WGS (Table 4). Two (20%) of these participants were verified to have new infections at the TOC (Fig. 1, Table 4), that is, the pretreatment and posttreatment isolates differed by 4119 and 1272 SNPs, respectively, despite that they both reported that they had abstained from sex between treatment and TOC. However, the remaining 8 (80%) participants were confirmed as treatment failures (i.e., their pretreatment and posttreatment isolates were indistinguishable [0–1 SNP difference] and had no significant differences in their MIC of examined antimicrobials; Table 4), and all 8 reported that they had abstained from sex between treatment and TOC.

DISCUSSION

In Malawi, gentamicin 240 mg IM and doxycycline 100 mg twice daily for 7 days have been used as the first-line treatment of urogenital gonorrhea for more than 25 years.[17] Among 141 gonococcal isolates from men with urethritis, 80% of gentamicin Etest MICs were ≤4 μg/mL with 100% ≤8 μg/mL, all below the WHO Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP)[28] alert value of >32.0 μg/mL. Compared with earlier studies in Malawi, Etest MICs from urethral specimens have consistently remained below 8 μg/mL despite reports of higher gentamicin MICs when using agar dilution.[17,18] South Africa[25] and Cote d'Ivoire[29] have reported higher Etest MICs ≥8 μg/mL from genital specimens with some isolates above the EGASP alert value. Generally, MICs have not always been predictive of gonorrhea clinical failure for most antimicrobials.[11,21] Without standardized methodology and interpretive criteria for determining gentamicin MIC

TABLE 2. Enrollment and Test of Cure (TOC) Gentamicin Etest MIC Results

Gentamicin Etest MIC, μg/mL	Enrollment, n (%)	TOC, n (%)
Total	141	13
2	2 (1.4)	1 (7.7)
4	111 (78.7)	8 (61.5)
8	28 (19.9)	4 (30.7)

MIC indicates minimum inhibitory concentration.

TABLE 3. Treatment Failure Week 1 MIC Distribution

Week 1 Result (n = 151)	Participants
Treatment success	135 (89.4%)
Treatment failure: Etest MIC 2 μg/mL	1 (0.1%)
Treatment failure: Etest MIC 4 μg/mL	8 (5.3%)
Treatment failure: Etest MIC 8 μg/mL	4 (2.6%)
Treatment failure: Etest MIC unknown	3 (2.0%)

MIC indicates minimum inhibitory concentration.

clinical resistance breakpoints, surveillance and AMR monitoring and comparisons remain a challenge.

To address this limitation, we incorporated a clinical TOC 1 week after treatment and estimated a minimum cure rate of male gonococcal urethritis of 89%. This cure rate can be compared with gentamicin clinical cure rates in Malawi of 95% in 1993 and 92% in 1996.[17] Gentamicin is used in dual treatment with doxycycline, which has activity against wild-type *N. gonorrhoeae*. However, we do not consider this substantially obscures our results of treatment, because of its universal resistance to *N. gonorrhoeae*. A systematic review of gentamicin clinical cure rates mostly for urogenital gonorrhea reported in 2014 global cure rates of 62% to 98%.[30] However, clinical cure rates are always limited by potential misclassification of reinfections as treatment failures, and vice versa. To mitigate this bias, we used genome-wide SNP analysis of the pretreatment and posttreatment isolates. Among the 10 participants with suspected treatment failures and viable pretreatment and posttreatment isolates, 2 matched isolates were different gonococcal strains based on the SNP analysis, thus indicating reinfection, whereas the remaining 8 matched pairs were within 1 SNP of their corresponding isolate, confirming treatment failure according to criteria from the European Centre for Disease Prevention and Control and WHO. All these 8 participants also reported abstaining from sex between treatment and their TOC, further verifying treatment failures. However, given that all participants were counseled to abstain from sex after treatment as part of their enrollment visit, and both participants with SNP proven new infections also reported abstaining from sex, social desirability bias likely played a role in participants' reported sexual behavior. Accordingly, a reinfection with the same gonococcal strain, for example, from the same sexual contact, can never be completely excluded.

Incorporating symptom information also adds context to our estimated clinical cure rate. Of those *N. gonorrhoeae* culture-positive at TOC, 8 of 16 (50%) reported elimination of symptoms after treatment and were asymptomatic at week 1 visit, potentially suggesting partial treatment or cure followed by reinfection or a completely new infection acquired during the incubation period. Among the 8 who were symptomatic at week 1 visit and who were asked about symptom resolution (n = 6), 1 (17%) participant reported no reduction in symptoms, which likely indicated treatment failure, whereas the remaining 5 of 6 (83%) reported symptom abatement followed by the return of a urethral discharge, potentially suggesting partial treatment, treatment failure, or reinfection. In total, only 1 of the 16 *N. gonorrhoeae* culture-positive at TOC self-reported having sex in the week after treatment.

The gentamicin efficacy for treatment of male gonococcal urethritis in Malawi is approximately 91% based on culture results at the TOC and SNP findings, which indicates that gentamicin alone or given in combination with doxycycline should be reassessed for first-line treatment. Recent trial results of gentamicin given in combination with azithromycin 1 g in the United Kingdom have shown higher cure rates (94%) for urogenital *N. gonorrhoeae* infection, which may also reflect the activity of azithromycin 1 g on gonococci, but poor cure rates for extragenital (pharyngeal [80%] and rectal [90%]) infections, concluding that gentamicin cannot replace ceftriaxone as first-line therapy for gonorrhea.[14] Our trial did not enroll women or test for any extragenital sites (i.e., rectal or pharyngeal), and including these will be crucial for future *N. gonorrhoeae* surveillance in Malawi. However, we were able to test a large sample size of male participants with urethritis leading to relatively precise and reliable estimates. Without a complete picture of gentamicin efficacy among women and extragenital sites in Malawi and the reported low efficacy in extragenital sites from other countries and the 89% clinical cure rate and universal doxycycline resistance found in our study, gentamicin and doxycycline should be reassessed as first-line treatment in Malawi.

We also assessed susceptibility to other antibiotics including ceftriaxone and azithromycin, which is the current recommended first-line treatment globally. Our results show 100% susceptibility to both drugs despite global reports of emerging and growing resistance to these antimicrobials.[10–12] Resistance in *N. gonorrhoeae* to ceftriaxone monotherapy and dual therapy with azithromycin or doxycycline has been reported in several countries.[11] Within Africa, decreased susceptibility or resistance to ceftriaxone has been reported in South Africa and Uganda.[11] Increasing resistance to azithromycin has been reported in many countries globally[10,11] resulting in the United Kingdom and United States recently recommending removal of azithromycin from its first-line therapy.[7,31] In Africa, azithromycin resistance (≥5%) has been reported in Cote d'Ivoire, Kenya, South

TABLE 4. Matched Gentamicin Etest MIC Results and Whole-Genome Sequencing for Those With Viable Enrollment and Test of Cure Culture (n = 10)

	Enrollment	Test of Cure		Comparison	
Participant	Etest MIC Result, μg/mL	Etest MIC Result, μg/mL	Urethritis Diagnosis	SNPs Between Pretreatment and Posttreatment Isolates	Interpretation
1	4	4	No	4119	New infection
2	4	8	No	1272	New infection
3	4	4	No	1	Treatment failure*
4	4	4	Yes	0	Treatment failure*
5	4	4	Yes	1	Treatment failure*
6	4	4	Yes	1	Treatment failure*
7	8	4	Yes	0	Treatment failure*
8	8	8	No	0	Treatment failure*
9	8	8	No	0	Treatment failure*
10	Unknown	8	Yes	1	Treatment failure*

*Reinfection with the same gonococcal strain can never be completely excluded.

MIC indicates minimum inhibitory concentration; SNP, single-nucleotide polymorphism.

Africa, and Uganda.[11] Compared with previous AMR surveys in Malawi, 12.6% of isolates were azithromycin resistant in 2016,[11] whereas no resistant isolates were found in 2007.[18]

In most countries, *N. gonorrhoeae* resistance to ciprofloxacin is exceedingly high, with some countries reporting >90% resistance.[10–12] In Africa, Cote d'Ivoire and South Africa have reported ≥70% resistance.[11] Compared with previous AMR surveys in Malawi, decreased susceptibility or resistance to ciprofloxacin increased from 1% in 2007[18] to ≥70% in 2016[11] but has slightly decreased to 63.1% in our study, making our results consistent with regional/global data (45.4%–94.0%).[11] Similarly, *N. gonorrhoeae* resistance to tetracyclines in Malawi has remained very high since the 1990s.[17] The sustained high tetracycline resistance likely indicates that the decline in clinical cure rates could be attributable to increasing gentamicin resistance.

Although AMR profiles are key determinants for treatment guidelines, other practicalities will have important ramifications for the successful implementation of any new treatment recommendations in Malawi. Gentamicin and doxycycline have been readily available, with only sporadic stock outs, and are inexpensive, making them reliable and feasible first-line drugs. Inconsistent drug pipelines and the potential for stock-outs for ceftriaxone and azithromycin may become highly problematic, whereas a higher cost could render any new drug option impractical.

The current cost of one dose of gentamicin (240 mg IM single dose) and doxycycline (100 mg BID for 7 days) in Malawi is approximately US $0.70.[32] In comparison, the cost of a single treatment per current WHO guidelines (ceftriaxone 250 mg IM single dose and azithromycin 1 g PO single dose) is approximately US $1.20. This cost difference, although appearing minor per individual dose, could present challenges for Malawi when acquiring drugs at the national level. In addition, because ceftriaxone is commonly used to treat severe bacterial infections in Malawi, using ceftriaxone to treat uncomplicated gonorrhea would require strict antimicrobial stewardship to avoid rapid resistance development.

Cefixime (400 mg PO single dose) dual therapy with azithromycin (1 g PO single dose; approximately US $1.80) might also be a possible alternative treatment. However, cefixime is not included in the Malawi essential medicines list,[33] and the cost could be prohibitive. Furthermore, cefixime and azithromycin both being tablets could be easily abused leading to ESC and azithromycin resistance. Lastly, spectinomycin is not effective in treating oropharyngeal gonorrhea, it has a high potential to develop resistance[20] and it is not widely available in Malawi limiting its use. We anticipate that gentamicin will continue to be widely used as the second-line drug for the syndromic treatment of urethritis in men and abnormal vaginal discharge and lower abdominal pain in women in Malawi.

We surveyed symptomatic men with *N. gonorrhoeae* urethritis seeking treatment at an STI clinic to determine the susceptibility profile of *N. gonorrhoeae* in Lilongwe, Malawi. Our results show that, although the in vitro MICs of gentamicin can suggest that the drug is still highly effective, clinical failures to cure male gonococcal urethritis are detected. Accordingly, gentamicin MICs poorly predict gonorrhea treatment outcome with gentamicin, which is likely due to suboptimal pharmacokinetic/pharmacodynamic parameters for gentamicin in the treatment of gonorrhea. The first-line gentamicin plus doxycycline treatment of gonorrhea in Malawi should be reassessed. We recommend routine surveillance of *N. gonorrhoeae* AMR in Malawi through the WHO EGASP programs to inform treatment guidelines. Clinical trials assessing *N. gonorrhoeae* drug susceptibility to different drug combinations in Malawi would be equally important.

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