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MAJOR ARTICLE

Effect on the Resistome of Dual vs Monotherapy for the Treatment of *Neisseria gonorrhoeae*: Results From a Randomized Controlled Trial (ResistAZM Trial)

Vanbaelen Thibaut,[1] Florence Eric,[1,2] Van Dijck Christophe,[1] Tsoumanis Achilleas,[1] Jolein Gyonne Elise Laumen,[1] Manoharan-Basil Santhini Sheeba,[1] Abdellati Saïd,[1] Tessa De Block,[1] De Baetselier Irith,[1] Van den Bossche Dorien,[1] Van Herrewege Yven,[1] Rotsaert Anke,[3] and Kenyon Chris[1]

[1]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, [2]Department of General Internal Medicine, Infectious Diseases and Tropical Medicine, University Hospital of Antwerp, Antwerp, Belgium, and [3]Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium

Background. No randomized controlled trial (RCT) has compared the impact on the resistome of ceftriaxone (CRO) plus azithromycin (AZM) vs CRO for the treatment of *Neisseria gonorrhoea* (NG).

Methods. This was an open-label, single-center, RCT comparing the effect on the resistome of CRO plus AZM vs CRO for the treatment of NG. Men who have sex with men (MSM) with genital, anorectal, or pharyngeal NG infection were randomized into the CRO/AZM and CRO arms. Oral rinse and anorectal samples were taken for culture and resistome profiling at 2 visits (baseline and day 14). The primary outcome was the ratio of mean macrolide resistance determinants in anorectal samples from day 14 between arms.

Results. Twenty individuals were randomized into the CRO/AZM arm and 22 into the CRO arm. We found no significant difference in the mean macrolide resistance determinants in the day 14 anorectal samples between arms (ratio, 1.05; 95% CI, 0.55–1.83; $P = .102$). The prevalence of baseline macrolide resistance was high (CRO/AZM arm = 95.00%; CRO arm = 90.91%).

Conclusions. We could not demonstrate a significant effect of dual CRO/AZM therapy on the resistome compared with CRO alone, likely due to a high baseline resistance to AZM. Interventions to prevent the emergence of antimicrobial resistance in MSM are needed.

Keywords. antimicrobial resistance; macrolide; men who have sex with men; *Neisseria gonorrhoeae*; resistome.

Neisseria gonorrhoeae (NG) has developed resistance to all antimicrobials used against it, and there are concerns that it might become untreatable in the near future [1]. One important mechanism in the development of antimicrobial resistance (AMR) in NG is the uptake of genetic material through transformation [1, 2]. Several studies have shown that NG acquired cephalosporin, sulfonamide, and macrolide resistance genes from commensal *Neisseria* species (spp.) [1, 3]. Commensal *Neisseria* spp. are much more prevalent than pathogenic *Neisseria* spp. [4]. As a consequence, they face a greater selection pressure than pathogenic *Neisseria* spp. to develop AMR if exposed to high levels of antimicrobials in a population [4]. AMR determinants from commensal *Neisseria* spp. can subsequently be transferred to NG under antimicrobial pressure [1]. Worryingly, AMR in commensal *Neisseria* spp. has been increasing in multiple countries, an effect that has been most pronounced in the populations most exposed to antimicrobials, such as men who have sex with men (MSM) taking HIV preexposure prophylaxis (PrEP) [5, 6].

There are currently 2 main options for the treatment of NG: monotherapy with ceftriaxone (CRO) or dual therapy with CRO plus azithromycin (CRO/AZM) [7–9]. Dual therapy emerged in the early 2010s and has been endorsed by the United States Centers for Disease Control and Prevention (CDC) and the European International Union against Sexually Transmitted Infections (EIUSTI) [7, 9]. The rationale behind dual therapy was based on the opinion of certain experts that it would delay the emergence of AMR in NG [10]. Importantly, to our knowledge, no randomized controlled trial (RCT) has compared the efficacy of mono with dual therapy. However, 2 recent meta-analyses did not find a significant difference in the eradication of pharyngeal or anorectal NG between the 2 options [11, 12]. In recent years, several guidelines, including those from the CDC and EIUSTI, have changed their recommendations to endorse monotherapy as the preferred or alternative treatment [7–9]. The main reason

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Correspondence: Thibaut Vanbaelen, MD, Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium (tvanbaelen@itg.be).

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for this switch is that the percentage of NG isolates with resistance to AZM has dramatically increased. In Belgium, for example, the proportion of clinical isolates with AZM resistance increased from 0.2% to 33% between 2013 and 2022 [13]. Similar trends have been described in other countries [7, 8]. These trends have been driven primarily by the emergence and spread of gonococcal clones with mosaic sections of their MtrCDE efflux pumps acquired from commensal *Neisseria* spp. [3, 14–18]. Studies have found that these clones are prevalent in core groups such as HIV-PrEP cohorts [17].

This has generated the hypothesis that dual therapy is partially responsible for the recent increase in gonococcal resistance to macrolides. The high levels of macrolides used in populations such as PrEP cohorts would have directly selected for macrolide resistance in commensal *Neisseria* spp. via bystander selection [19]. Because azithromycin has a long tissue half-life, its long post-therapy tail could also have provided a selective advantage for gonococcal strains to acquire macrolide resistance from commensal *Neisseria* spp. in populations with intense AZM exposure [20]. While the available evidence suggests there is equipoise in the efficacy of both dual and monotherapy for the treatment of NG [11], no study that we are aware of has evaluated the effect on the resistomes. In this paper, we present the results of an RCT that assessed the impact on the resistome of both therapeutic regimens. We hypothesized that the receipt of CRO/AZM results in a greater increase in macrolide resistance genes in the anorectal resistome and in macrolide resistance in oropharyngeal commensal streptococci and *Neisseria* spp. than CRO.

METHODS

Study Design, Setting, and Participants

We performed an open-label, single-center RCT to compare the effect on the resistome of CRO plus AZM dual therapy (CRO/AZM) vs CRO monotherapy for the treatment of NG. The study took place at the HIV/STI clinic of the Institute of Tropical Medicine (ITM) in Antwerp, Belgium. Individuals with a diagnosis of symptomatic or asymptomatic genital, anorectal, or pharyngeal NG detected in routine care were approached for the study. Inclusion criteria were being able and willing to provide written informed consent, being assigned male sex at birth, being at least 18 years old, and having a confirmed diagnosis of urethral, anorectal, or pharyngeal NG by molecular detection or, for patients with urethritis, a gram/methylene blue stain of a urethral smear showing intracellular diplococci and >10 white blood cells/field. Exclusion criteria were the use of any macrolide antibiotics in the previous 6 months, a known contraindication or allergy to ceftriaxone, azithromycin, or lidocaine, and the presence of any other condition, including the suspicion or diagnosis of sexually transmitted infections (STIs), that required the administration of an antibiotic other than CRO at enrollment.

Randomization

Subjects who met all the inclusion and exclusion criteria were randomized with a 1:1 ratio into the CRO/AZM and CRO study arms. The randomization list was prepared by an independent sponsor biostatistician using SAS 9.4 (SAS Institute, Cary, NC, USA) and was not shared with the study team until the database was locked.

Study Procedures

Two study visits were planned—a baseline visit and a follow-up visit at day 14 (+/− 1 day).

During the baseline visit, we collected a sample from the site where NG was detected for NG culture. In addition, we collected oral rinse samples [21] using 15 mL of sterile phosphate-buffered saline (PBS; Oxoid, Dulbecco A) for culturing oropharyngeal streptococci and *Neisseria* spp. and anorectal swabs (Eswab medium, COPAN Diagnostics Inc., Brescia, Italy) for resistome profiling. Urine samples were collected by the patient. Oral rinse samples were self-collected under the supervision of the study physician after having received instructions. The oral rinse samples were stored at −80°C using skim milk with 30% glycerol. For the anorectal swabs, participants could opt for self-collection or collection by the study physician.

Data were collected on STI history, HIV status, HIV-PrEP use, number of sex partners (past 3 months), and antibiotic use (past 12 months). An oral examination was performed, and a physical examination if deemed necessary. Participants then received their allocated treatment. In the CRO/AZM group, participants received ceftriaxone 1 g single-dose intramuscularly (IM) and azithromycin 2 g single-dose orally under the supervision of the study physician. Participants in the CRO group received ceftriaxone 1 g single-dose IM alone.

At the day 14 visit, samples from the previously infected sites were taken for molecular detection and culture to assess the NG clearance as part of routine care. In addition, we collected oral rinse samples for streptococci and *Neisseria* spp. culture and anorectal swabs for resistome profiling, as described above. Data were collected on HIV status, HIV-PrEP use, and antibiotic use since the last visit.

Laboratory Procedures

NG molecular testing was performed using the Abbott RealTime CT/NG assay. Positive NG samples were confirmed using in-house real-time polymerase chain reaction (PCR) [22]. NG was cultured on GC selective agar (Becton Dickinson, Heidelberg, Germany), and, if positive, antimicrobial susceptibility testing of ceftriaxone, ciprofloxacin, and azithromycin was done using Etests (BioMérieux, France).

Culture of oral commensal *Neisseria* spp. and streptococci was performed with and without azithromycin (2 μg/mL), according to Laumen et al. (Supplementary Appendix p.1) [21].

Shotgun Metagenomic Sequencing and Bioinformatic Analyses

The anorectal swabs were shipped on dry ice to Eurofins Genomics for DNA isolation, library preparation, and metagenomic sequencing. The raw sequencing data have been deposited with links to BioProject accession number PRJNA974953 in the NCBI BioProject database (https://www.ncbi.nlm.nih.gov/bioproject/). Bioinformatic analyses were carried out according to Van Dijck et al. (Supplementary Appendix p.1) [23].

Outcomes

In this paper, we defined macrolide resistance as resistance to macrolides, lincosamides, and streptogramins. The primary outcome was the ratio of mean macrolide resistance determinants in the day 14 visit anorectal samples between the 2 treatment arms. This ratio was calculated by dividing the mean normalized read count of macrolide resistance determinants categorized at the class level (macrolides, lincosamides, and streptogramins) in the CRO/AZM group by the corresponding mean normalized read count in the CRO group. We also calculated the proportion of individuals carrying macrolide resistance genes. For that purpose, any measurement in the normalized macrolide resistance determinants above 0 was deemed macrolide resistance.

The secondary outcomes also included the ratio of mean resistance determinants applied to each nonmacrolide antibiotic class in the day 14 visit anorectal samples. Additionally, 3 indicators of multidrug resistance were created. The first indicator represented participants who carried resistance genes to >1 of the following nonmacrolide antibiotics: aminoglycosides, beta-lactams, fluoroquinolones, and tetracyclines. A second indicator was created with the addition of trimethoprim and sulfonamides to the previous indicator. A third indicator represented participants who carried resistance genes to both macrolides and nonmacrolides.

Based on culture results, the difference in the proportion of oropharyngeal commensal *Neisseria* and streptococci that are macrolide resistant between the 2 treatment arms at both visits was calculated by dividing the number of colonies on the plates containing azithromycin by the number of colonies on the plates without azithromycin. Lastly, an indicator representing the proportion of individuals presenting ≥1 resistant colony, for streptococci and commensal *Neisseria* spp. separately, at baseline was created.

The primary analysis was performed using the intention-to-treat (ITT) approach. In the ITT analysis, all randomized participants who gave ≥1 sample on day 14 were analyzed according to their randomized allocation, even if they received another intervention, showed protocol violations before or during the study, or were lost to follow-up. In the per-protocol analysis, only participants who received the intervention and followed the protocol as planned were included.

Statistical Analysis

Assuming a 2.5-fold increase in the ratio of macrolide resistance determinants in the CRO/AZM group compared with the CRO group, a sample size of 42 patients was estimated to detect this effect size at a significance level of .05 and with a power of 80%. The rationale behind this effect size estimation was based on a previous study, the MORDOR trial, which found a 7-fold increase in this ratio following repeated mass administration of AZM in Niger [24]. Given the difference in the study populations between our study and the MORDOR trial, we used a much lower effect size. Our sample size calculation was corrected for a dropout rate of 5%.

We described baseline characteristics using medians and interquartile ranges for continuous variables and absolute numbers and proportions for categorical variables.

The primary analysis of assessing the ratio of the mean normalized macrolide resistance determinants in the anorectal microbiome between the 2 arms was done using a permutation test with 10 000 permutations. The normalized macrolide resistance read counts were calculated by dividing the number of macrolide resistance reads by the total number of bacterial reads in the sample. The resulting proportion was then multiplied by 10^6 to generate normalized resistance read counts per million reads. A 95% CI for the ratio of the 2 arms was estimated using permutation. In cases where multiple comparisons were made, the *P* values were adjusted using the Benjamini-Hochberg method for family-wise error. The secondary analysis regarding mean normalized resistance read counts of nonmacrolide antibiotic class in anorectal samples was done similarly.

Proportions are presented with Wilson's 95% CIs and compared using the Fisher exact test. The latter was also used to compare the patient count with adverse events in the 2 arms. Means and medians were compared using the Mann-Whitney *U* test and, for paired samples, the Wilcoxon signed-rank test. No subgroup nor interim analysis was performed. All computations were made using R, version 4.2.3 [25].

Ethical Clearance and Trial Registration

All participants provided written informed consent at baseline. The Institutional Review Board of the ITM, the Ethics Committee of the University Hospital of Antwerp, and the Competent Authorities of Belgium (FAMPH) approved the trial. The study was carried out in compliance with the Declaration of Helsinki and according to the most recent Good Clinical Practice guidelines. It was registered in the EudraCT public registry (EUDRACT 2021-003616-10).

RESULTS

Between January 17 and May 9, 2022, a total of 64 individuals were approached for the study. Twenty-two were not included

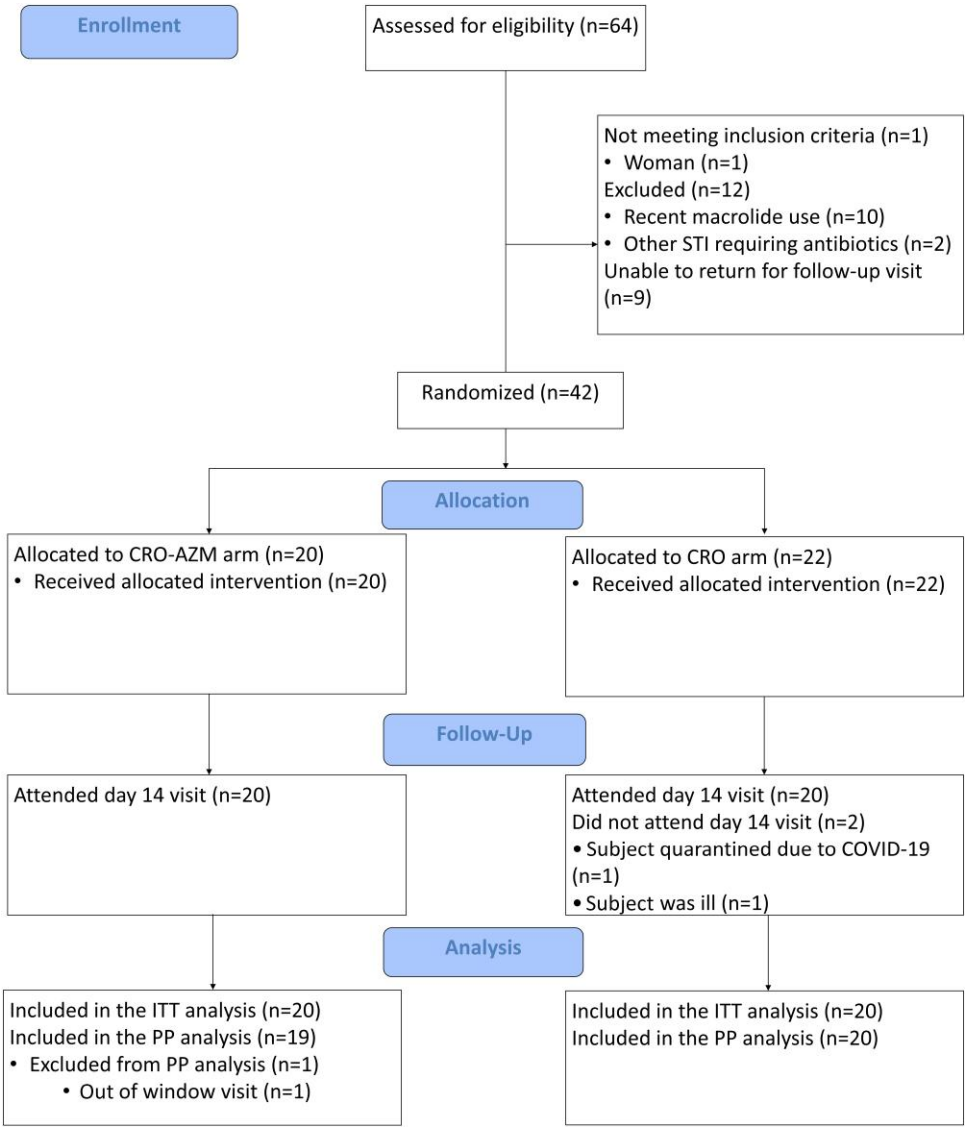

Figure 1. Trial profile. Abbreviations: AZM, azithromycin; COVID-19, coronavirus disease 2019; CRO, ceftriaxone; ITT, intention-to-treat; PP, per protocol; STI, sexually transmitted infection.

due to not meeting the inclusion and/or exclusion criteria or due to not being able to return for the day 14 visit (Figure 1). The remaining 42 individuals were randomized (22 to the CRO arm and 20 to the CRO/AZM arm). Two participants in the CRO arm were excluded from the ITT analysis as they did not attend the day 14 visit.

All participants were male. The median age at baseline (interquartile range [IQR]) was 40 (29.3–44.0) years (Table 1). A total of 9 (9/42, 21.43%) participants reported being HIV positive, and 27 (27/42, 64.29%) reported taking HIV-PrEP. Participants had a median (IQR) of 5 (3–8.25) sex partners in the past 3 months, and 18 (18/42, 42.86%) used antibiotics in the past 12 months. Sociodemographic and sexual risk-taking characteristics were well balanced between both arms (Table 1).

In the primary analysis, the mean normalized macrolide resistance determinants count in anorectal samples at day 14 was 110.3 counts/million reads (95% CI, 64.54–156.06) in the CRO arm and 167.53 counts/million reads (95% CI, 97.86–237.19) in the CRO/AZM arms (Table 2). Their ratio was not statistically significant (ratio, 1.05; 95% CI, 0.55–1.83; $P = .102$) (Table 2, Figure 2). Likewise, there was no statistically significant difference in non–macrolide lincosamides streptogramines determinants in anorectal samples on day 14 between the 2 arms (Table 2). The proportions of participants with macrolide resistance were 90.91% (95% CI, 76.39%–99.11%) in the CRO arm and 95.00% (95% CI, 76.39%–99.11%) in the CRO/AZM arm at day 0, and 100% (95% CI, 83.89%–100%) in both arms at day 14. These differences were not statistically significant.

The proportions of participants with multidrug resistance at day 14 were not statistically significant between both arms (Supplementary Appendix p.2).

Based on culture results, the mean proportion of streptococci/commensal *Neisseria* spp. that were macrolide resistant at day 0 was 66.66%/51.40% in the CRO arm and 68.61%/48.64% in the CRO/AZM arms, respectively (Supplementary Appendix p.3–4). At day 0, 100% (95% CI, 89.75%–100%) of individuals had ≥1 macrolide-resistant *Streptococcus* colony, and 92.50% (95% CI, 74.4%–95.20%) had ≥1 macrolide-resistant commensal *Neisseria* spp. colony (Supplementary Appendix p.5).

Similar results were obtained in the per-protocol analysis (Supplementary Appendix p.6).

A total of 6 participants reported adverse events deemed drug-related by the investigators (Supplementary Appendix p.7). No serious adverse event was reported. No difference between both arms was found in terms of adverse events.

Table 1. Sociodemographic, Sexual Risk Taking, and Characteristics of *Neisseria gonorrhoeae* Infection at Baseline[a]

…	CRO (n = 22), No. (%)/Median (IQR)	CRO/AZM (n = 20), No. (%)/Median (IQR)	Total Sample (n = 42), No. (%)/Median (IQR)
Age, y	40 (28.5–41.75)	41.5 (29.75–45)	40 (29.25–44)
HIV status			
Positive	5 (22.73)	4 (20)	9 (21.43)
Negative	17 (77.27)	16 (80)	33 (78.57)
No. of partners (last 3 mo)	5 (3–6)	5 (3.75–10)	5 (3–8.25)
Use of antibiotics (last 12 mo)	8 (36.36)	10 (50)	18 (42.86)
Amoxicillin/clavulanic acid	0 (0)	2 (10)	2 (4.76)
Ceftriaxone	0 (0)	0 (0)	0 (0)
Doxycycline	0 (0)	0 (0)	0 (0)
Penicillin	0 (0)	0 (0)	0 (0)
PrEP use: yes	14 (63.64)	13 (65)	27 (64.29)
NG infection			
Symptomatic	7 (31.82)	6 (30)	13 (30.95)
Asymptomatic	15 (68.18)	14 (70)	29 (69.05)
NG infection site			
Anorectal	2 (9.09)	1 (5)	3 (7.14)
Urethral	4 (18.18)	5 (25)	9 (21.43)
Pooled (urethral, anorectal, pharyngeal)	16 (72.73)	14 (70)	30 (71.43)

Abbreviations: AZM, azithromycin; CRO, ceftriaxone; IQR, interquartile range; NG, *Neisseria gonorrhoeae*; PrEP, pre-exposure prophylaxis.

[a]There was no statistical difference between the 2 arms in any of these variables.

DISCUSSION

Our study did not show a difference in the abundance of macrolide and nonmacrolide resistance determinants in anorectal samples 14 days after administration of CRO or CRO plus AZM. The prevalence of macrolide resistance was high at baseline and remained high at day 14 in both arms. The prevalence rates of multidrug resistance on day 14 were similar between both arms.

These findings contrast with the results of previous studies. An RCT compared phenotypic macrolide resistance in oropharyngeal streptococci after a course of azithromycin or clarithromycin vs placebo among >200 healthy volunteers in Belgium [26]. This study showed a large increase in macrolide resistance from ∼30% to 80% in both intervention arms and no increase in the placebo arm. The increase in macrolide resistance persisted throughout the study, up to 180 days. A cluster RCT among children in Niger evaluated the effect on the resistome of 6-monthly mass azithromycin distribution vs placebo for a total study duration of 4 years [24]. This study found that azithromycin had a pronounced effect on pheno- and

Table 2. Primary Analysis Results, Comparison of Mean Read Counts of Normalized Macrolide and Nonmacrolide Resistance Determinants in Anorectal Samples at Day 14 (Intention-to-Treat Analysis)

…	CRO + AZM (95% CI)	CRO (95% CI)	Ratio (CRO + AZM/CRO) (95% CI)	*P* Value
Determinants	…			
MLS	167.53 (97.86–237.19)	110.3 (64.54–156.06)	1.05 (0.55–1.83)	.1026
Aminoglycosides	22.22 (14.98–29.46)	34.41 (11.36–57.45)	1.12 (0.47–2.19)	1
Beta-lactams	89.82 (68.36–111.28)	110.46 (80.17–140.76)	1.01 (0.69–1.44)	1
Bacitracin	1.11 (0–2.96)	4.63 (0–11.21)	3.79 (0.05–20.15)	1
Glycopeptides	0.14 (0–0.4)	0.26 (0–0.77)	0.83 (0–1.91)	1
Trimethoprim	1.55 (0.4–2.69)	2.73 (0.7–4.77)	1.19 (0.32–3.15)	1
Cationic antimicrobial peptides	5.52 (0–14.65)	16.52 (0–38.45)	2.82 (0.07–14.64)	1
Mupirocin	0 (0–0)	0.84 (0–1.86)	1.49 (0–5.34)	1
Metronidazole	0.06 (0–0.19)	0.2 (0–0.61)	1.2 (0–3.22)	1
Fluoroquinolones	23.9 (0–68.13)	9.44 (0–21.97)	6.44 (0.02–46.02)	1
Sulfonamides	0.62 (0–1.76)	5.47 (0–11.84)	10.6 (0.01–148.86)	1
Tetracyclines	423.8 (361.52–486.09)	348.12 (286.41–409.82)	1.01 (0.79–1.27)	.5621

Abbreviations: AZM, azithromycin; CRO, ceftriaxone; IQR, interquartile range; MLS, macrolide lincosamides streptogramines.

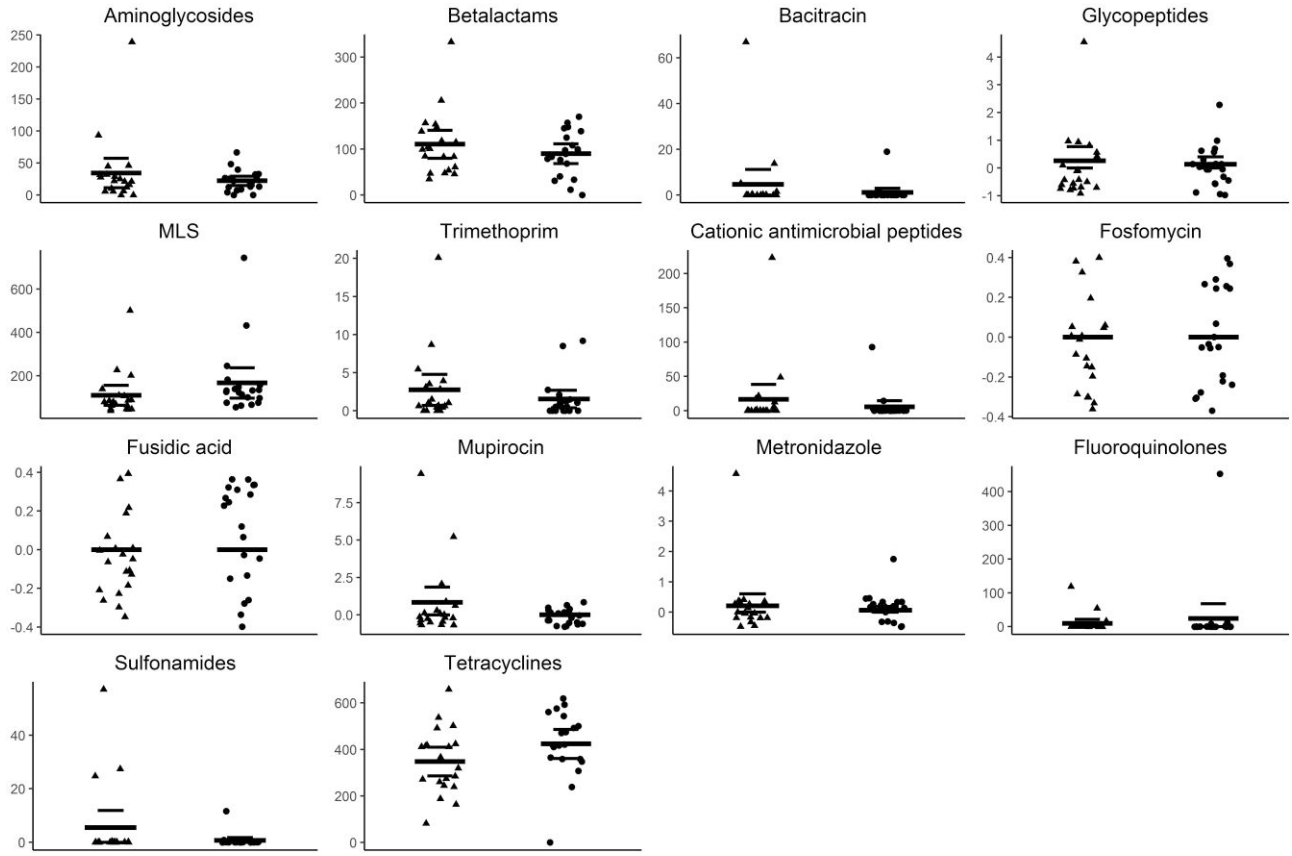

Figure 2. Normalized abundance of resistance determinants (reads/million) at day 14 by treatment arm in reads per million (triangle: CRO; circle: CRO/AZM). Points represent actual measurements, elongated horizontal lines represent means, and shorter horizontal lines represent the lower and upper bounds of the 95% CI. Abbreviations: AZM, azithromycin; CRO, ceftriaxone; MLS, macrolide lincosamides streptogramines.

genotypic resistance. The prevalence of resistance to erythromycin in oral streptococci increased to a mean of 12.3% in the azithromycin arm compared with 2.9% in the placebo arm [27]. Likewise, a substantial increase in the abundance of genes conferring macrolide and nonmacrolide resistance in the gastrointestinal tract was seen in participants receiving azithromycin. Participants in the intervention arm had 7.5 times more macrolide resistance determinants than those in the placebo arm at the end of the trial [27].

The discrepancy between our results and those of previous studies might be attributed to the different prevalence rates of macrolide resistance at baseline. While considerable caution should be exercised in comparisons between studies using different methodologies, the proportion of individuals with phenotypic macrolide resistance in oral streptococci in our study at baseline (100% in both arms) was considerably higher than the 2.9% in the Niger study [24]. The prevalence of macrolide resistance in commensal *Neisseria* spp. in our study at baseline was also high, >90% in both arms. In a similar vein, the mean proportion of streptococci/commensal *Neisseria* spp. that were macrolide resistant at day 0 (around 50% and 70%, respectively) was higher in our study than the 30% baseline macrolide resistance found in streptococci in the Belgian volunteer study [26].

The high prevalence of macrolide resistance in both commensal *Neisseria* and streptococcal species found in our study is alarming for a number of reasons. The prevalence of macrolide resistance has been increasing not only in NG but also in invasive streptococcal infections [28]. As already noted, the rapid increase in macrolide resistance in NG has been driven by NG lineages that have acquired mosaic MtrCDE efflux pumps from various commensal *Neisseria* spp. [3, 14–18]. A number of authors have argued that antimicrobial resistance in commensal *Neisseria* serves as a critical early warning system of excess antimicrobial consumption and risk of AMR emerging in the pathogenic *Neisseria* species [4, 20].

These findings also suggest that a saturation of macrolide resistance determinants in our study population before the intervention may explain the lack of an effect of dual therapy on macrolide resistance. The very high prevalence of resistance to macrolides at baseline we found might be explained by intensive antimicrobial consumption in our study population. About

40% of the participants reported use of antimicrobials in the 12 months before the baseline visit. The use of antimicrobials is correlated with antimicrobial resistance in several pathogens, such as NG and *Streptococcus pneumoniae* [29, 30]. We have previously shown that macrolide consumption in a Belgian PrEP cohort was 52-fold higher than the community-level consumption of certain European countries. Moreover, this macrolide consumption exceeds thresholds known to be associated with high rates of AMR in *Mycoplasma genitalium*, *Treponema pallidum*, and *Streptococcus pneumoniae* by 5- to 9-fold [31, 32]. Likely as a result of this intense consumption, the prevalence of macrolide resistance in *Treponema pallidum* and *Mycoplasma genitalium* in MSM attending our STI clinics is over 90% and 33.6% in *N. gonorrhoeae* [13, 33, 34]. Further evidence for the saturation hypothesis comes from a previous study that found very high levels of macrolide, fluoroquinolone, and cephalosporin resistance in oral commensal *Neisseria* spp. in MSM attending our STI clinic, but no difference between the groups who had, and had not, consumed antimicrobials in the preceding 6 months [6]. The prevalence of resistance to these antimicrobials in both groups was, however, considerably higher than that in the general population [6]. In addition, in this study, macrolide resistance–associated genes in the oropharynx were >2 times more abundant in MSM than in the general population [23].

These findings suggest the need for interventions to reduce antimicrobial consumption in populations at risk for the further emergence of AMR. We have calculated that dual therapy for NG and *Chlamydia trachomatis* (CT) infections is the major driver of macrolide consumption in our PrEP cohort [35]. Switching from dual to monotherapy for the treatment of NG might be a way to reduce macrolide consumption.

Our study has several limitations. First, we based our sample size calculation on a study performed on a different population. Although we tried to adapt to this difference by reducing the expected effect size, we cannot exclude that our study was underpowered to evaluate the effects in our population. Second, we assessed the impact of CRO/AZM vs CRO at only 1 time point, 14 days after the administration of the antimicrobials. Therefore, we cannot infer what the results would have been at other time points. Fourth, neither participants nor physicians were blinded, which might have led to altered behavior between the study visits.

Other types of evidence should be considered when choosing between monotherapy and dual therapy for the treatment of NG. As noted above, 2 systematic reviews of observational studies found no difference in efficacy at curing NG between monotherapy and dual therapy [11, 12]. In addition, a combined individual- and ecological-level analysis of determinants of gonococcal macrolide and cephalosporin minimal inhibitory concentrations (MICs) from >20 000 isolates in 26 European countries found that dual therapy was associated with a higher azithromycin MIC than monotherapy, and no difference was found in ceftriaxone MICs [36]. A key argument for the introduction of dual therapy is that the azithromycin would protect the ceftriaxone from the acquisition of resistance [10]. The available evidence does not support this supposition. Moreover, a number of studies have noted that the excess consumption of antimicrobials such as macrolides may exert much of the excess consumption of antimicrobials effects at the population level [37], and other studies have found that a population-level reduction in macrolide consumption effectively leads to a reduction in macrolide resistance in streptococci [38]. Together with the increasing prevalence of macrolide resistance, these findings have motivated the authors of certain guidelines to return to monotherapy as the preferred gonococcal treatment [7].

CONCLUSIONS

Our study did not find that dual therapy resulted in an increase in pheno- or genotypic macrolide resistance compared with monotherapy. This lack of increase might have been due to the high prevalence of macrolide resistance at baseline, which in turn was likely due to the high antimicrobial consumption in the study population. Previous studies have found that macrolide consumption leads to a substantial and prolonged increase in macrolide and nonmacrolide resistance determinants and that reducing macrolide consumption can reduce the prevalence of macrolide resistance. Switching from dual to monotherapy for NG is one way to achieve this. Despite the negative results of our study, we conclude that the evidence reviewed above, in combination with the observed high baseline levels of macrolide resistance in our study, supports the switch to monotherapy for NG.

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Patient consent. All participants provided written informed consent at baseline. The Institutional Review Board of the ITM, the Ethics

Committee of the University Hospital of Antwerp, and the Competent Authorities of Belgium (FAMPH) approved the trial.

Potential conflicts of interest. None declared.

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