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MAJOR ARTICLE

Switching From Dual to Monotherapy for Gonorrhea is Associated With a Halving of Gonococcal Resistance to Azithromycin—A Modelling Study of MSM in Belgium

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Background. *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are 2 of the most common bacterial sexually transmitted infections. The prevalence of azithromycin resistance in NG (AR-NG) has increased from 1% to 47.9% in the past 10 years among men who have sex with men (MSM) in Belgium. Dual therapy with ceftriaxone and azithromycin was until recently the standard-of-care in Belgium. Our objective was to reproduce the azithromycin-resistance epidemic among MSM in Belgium using dual therapy and to evaluate the counterfactual scenario of using ceftriaxone monotherapy on the emergence of AR-NG.

Methods. We developed a network-based model for CT and NG transmission among MSM in Belgium to estimate the prevalence of CT, NG, and AR-NG in the population. The model simulates transmission of NG among 3 anatomical sites in a population of 10 000 MSM over 10 years. The effect of different treatment strategies was evaluated in terms of CT, NG, and AR-NG prevalence as well as antibiotic consumption.

Results. Our model captured adequately well the observed azithromycin-resistance epidemic over a 10-year period in Belgium, with AR-NG increasing from 0% to 44%. Antibiotic consumption, and prevalences of NG and AR-NG decreased when ceftriaxone monotherapy was used against NG, while CT prevalence increased, compared to dual therapy. In the ceftriaxone monotherapy scenario, the prevalence of AR-NG was approximately half of that in the dual-therapy scenario (23%).

Conclusions. Switching from dual to monotherapy was associated with a halving of the prevalence of AR-NG. These results provide further evidence to favor mono- over dual therapy for the treatment of gonorrhea.

Keywords. antimicrobial resistance; *chlamydia trachomatis*; mathematical model; men who have sex with men; *neisseria gonorrhoeae*.

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) are 2 bacterial sexually transmitted infections (STIs) with an increasing incidence in many European countries [1, 2] and elsewhere [3, 4]. A further concern is that NG has developed resistance to all classes of antibiotics it has been exposed to, including the currently recommended therapies [5–7]. Almost half of the reported gonorrhea cases in European countries [1] (48%) and the United States [3] (47%) are attributed to men who have sex with men (MSM). Screening has been one of the interventions employed by many countries to tackle this issue [8], with a mindset of "search and destroy": the idea that detecting and treating more infections would result in lower incidence, lower antibiotic use, and ultimately, less antimicrobial resistance. Several national and international guidelines recommend at least annual screening for gonorrhea and chlamydia for sexually active MSM, and every 3 to 6 months in those at highest risk [8–14]. Currently, the European International Union Against STIs recommends dual treatment with a combination of ceftriaxone (a third-generation cephalosporin) and azithromycin (a macrolide antibiotic) as the recommended treatment for gonorrhea, with ceftriaxone monotherapy as an alternative [15]. The rationale for dual therapy was that it could prevent the emergence of ceftriaxone resistance in NG. There is, however, little evidence to back this up, and a number of countries have recently changed their treatment guidelines to ceftriaxone monotherapy [16–19]. One of the reasons for doing this was the concern that the azithromycin component of dual therapy was

Received 07 January 2025; editorial decision 27 May 2025; accepted 01 June 2025; published online 2 June 2025

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https://doi.org/10.1093/ofid/ofaf320

contributing to a syndemic of macrolide resistance in NG and other species [19]. For example, a study in Belgium found that the combination of screening for NG/CT and dual therapy resulted in a macrolide exposure up to 7-fold higher than resistance inducing thresholds in MSM taking preexposure prophylaxis (PrEP) [20]. The prevalence of gonococcal azithromycin resistance in MSM in Belgium has increased from 1% to 47.9% over the past 9 years during the time that dual therapy was used [21].

Furthermore, a recent study found that NG isolates from the only country in Europe that never switched from ceftriaxone monotherapy to dual therapy (the Netherlands) did not have greater increases in ceftriaxone minimum inhibitory concentrations (MICs) compared to countries that switched to dual therapy [22]. Rather, monotherapy in the Netherlands was associated with lower gonococcal azithromycin MICs compared to countries using dual therapy [22].

Similarly, a small randomized controlled trial found that dual therapy was associated with an increase in macrolide MICs in commensal *Neisseria* (CN) and streptococcal species [23]. It is unlikely that an adequately powered randomized controlled trial can be conducted that is able to compare the risks and benefits of mono- and dual therapy on antimicrobial resistance (AMR) in other bacterial species such as NG. In the absence of such a study, it would be useful to be able to use mathematical models to compare the effects of mono- and dual therapy on the emergence of macrolide resistance in NG.

Many modeling studies have attempted to describe the transmission of CT and NG among MSM [24–57]. The majority of the published models from Europe are compartmental models, with only a handful of models using individual-based or network models [24, 37, 45, 51, 56, 58]. Network models allow for a more complex and realistic structure of the contact network and behavioral characteristics (such as risk-taking, condom use, etc.), and are able to account for all 3 anatomical sites (oropharynx, urethra, and rectum) for transmission of CT and NG. A further limitation of previous modelling studies is that none of them have considered the commensal *Neisseria* species in the emergence of AMR. Because these species are universally present in the oropharynx, they are particularly susceptible to bystander selection of AMR (AMR induced by the use of antimicrobials for other indications) [59]. They can then pass on the resistance conferring DNA to NG via transformation when NG coinfects the oropharynx [60]. This mechanism has been shown to play a crucial role in the emergence of macrolide and cephalosporin resistance in NG [60, 61]. In this paper, we include the emergence of macrolide resistance in commensal *Neisseria* spp. and subsequent transformation into *N gonorrhoeae* with the aim of replicating the gonococcal azithromycin-resistance epidemic in the past decade among MSM in Belgium. We compare this with the counterfactual scenario of ceftriaxone monotherapy for NG.

METHODS

Overview

We developed a network model to describe the dynamics of CT and NG transmission and the emergence of azithromycin-resistance among MSM in Belgium. Separable Temporal Exponential-family Random Graph Models [62–64] were used to fit and simulate the structure of the sexual partnership network. The model was developed as an extension of our previous modeling work [56].

The parameters used to construct the network and inform the processes in the model come from a previous modeling paper [65], which used data from the Belgian-based participants of the European MSM Internet Survey 2017 [66]. Additionally, primary data from the PreGo study, a single-center, randomized crossover trial in Belgium [67], was used for parameters on CT and NG prevalence. Primary data from the Gonoscreen study [68], a randomized clinical trial to compare the effect of screening versus nonscreening on the incidence of CT and NG in MSM taking PrEP, was used for information on antibiotic use. Data on screening rates were estimated using the Sciensano 2021 report on the epidemiology of STIs in Belgium [69].

The individuals in the population were categorized into high and low activity, depending on their sexual activity and risk-taking behaviors. We estimated that 27.90% (26.23–29.64; 95% confidence interval [CI]) of the Belgian MSM population classified as high-activity MSM (HA-MSM) [65], which is similar to previously published studies from Belgium and Europe [70–72]. The remaining population in the network was classified as low-activity MSM (LA-MSM).

The model consisted of 3 parallel interacting networks representing steady, persistent casual, and 1-off (1-night stand) partnerships. Each individual in the network had 3 anatomical sites where CT and NG transmission could occur: pharynx, urethra, and rectum. All definitions, processes, and parameters are described in detail in the Online Supplement.

N Gonorrhoeae and *C Trachomatis* Transmission

At each time step, the number of sexual acts between 2 partners was calculated. Each sex act could be a combination of 6 sex types: oral, oro-anal, and anal sex, each of which could be insertive or receptive. Condom use was implemented during anal sex only, as the use of condoms during oral or oro-anal sex is uncommon [73–75].

Directional transmission of NG and CT occurred stochastically given the active partnerships, the number of sex acts within a pair, the sex type combinations, the sites involved within each act, and their respective NG/CT infection status, at each

time point. The per-act transmission probabilities (same for both groups) depended only on the sites involved, the sex role (insertive/receptive) of each partner, recent consumption of antibiotics, and condom use, which are different for CT and NG.

Appearance of symptoms was assumed to happen on the same time step; infected nodes were considered infectious on the next time step. Transmission and symptom probabilities were unavailable in the source data and were calibrated based on information from a literature review (Online Supplement).

Screening, Treatment, and Recovery

At each time step, individuals could be randomly selected among all eligible individuals to be screened for STIs. Eligibility for screening was determined by 2 criteria. Based on estimates from the European MSM Internet Survey 2017 data, 31.03% and 9.05% of the LR- and HR-MSM were assigned as persons who never screen for STIs and were subsequently removed from the pool of eligible individuals to be selected for screening. All remaining individuals would be deemed eligible for screening if they had not been selected for screening within the specified screening interval (3 months for HA- and 12 months for LA-MSM). The selection depended on the proportion of the group we assumed would attend a screening visit and the specified interval between 2 screening visits, which was different for each group (360 and 90 days for LA- and HA-MSM, respectively). We estimated that 36.3% of LA-MSM and 44.4% of HA-MSM screen at least annually for STIs [70, 76]. The proportions of anatomical sites tested during screening visits were estimated [65]. A diagnosis of CT/NG would be confirmed on a positive STI test result, due to presence of symptoms, or due to an STI screening visit. On diagnosis, all confirmed CT/NG cases would receive treatment, dual therapy with ceftriaxone and azithromycin (for gonorrhea), and azithromycin or doxycycline (for chlamydia), according to the previous Belgian treatment guidelines [77].

Infected, but untreated individuals would return to a susceptible state through natural clearance, which was modeled as a stochastic function with different recovery rates for each anatomical site and infection. Expected times for natural clearance were not available in the source data and were calibrated. The expected time to recovery of treated individuals was estimated to be 1 day [76, 78] for either infection, and were equal across all 3 anatomical sites.

Azithromycin Resistance Emergence and Commensal *Neisseria* Species

The role of commensal *Neisseria* spp. as a reservoir of antimicrobial resistance genes for pathogenic species, such as NG, is well documented [79–86]. In the model, we included the presence of CN in the oropharynx of the individuals in our network. We considered CN a single category, without differentiation among the different species. The ability to develop azithromycin resistance in CN and NG was represented by the MIC level, which was modeled as a categorical variable (0, 1: susceptible, 2, 3, 4: resistant). The MIC of the CN would increase by 1 level (with a fixed 100% probability) whenever individuals were exposed to azithromycin and would decrease by 1 level using a time-dependent decay probability based on time since last exposure to azithromycin.

Azithromycin resistance (AR) in NG could occur through 2 distinct and independent ways. Spontaneous emergence of AR-NG could occur to NG-infected individuals who were exposed to azithromycin, stochastically through a single Bernoulli draw with a fixed probability, at the time of treatment administration. This probability of spontaneous emergence of AR was invariant across NG infections at the three anatomical sites. Once spontaneous AR occurred, the MIC of the AR-NG was randomly allocated to 1 of the 3 resistance MIC levels.

The second option for AR emergence would be through horizontal gene transfer (HGT). In individuals who were infected with azithromycin-susceptible NG in the pharynx, HGT of macrolide resistance from the CN to the NG could occur through a single Bernoulli draw with a fixed probability at the time of the acquisition of the pharyngeal NG. NG would then take the resistance MIC level of the donor CN. Both probabilities for spontaneous resistance emergence and for HGT were not available in the literature and were calibrated.

Azithromycin resistant cases were assumed to be susceptible to dual therapy with a probability of 99% [87]. The remaining AR-NG–infected anatomical sites would switch to the uninfected state through natural clearance. In case of exposure only to azithromycin (eg, due to treatment given for a CT infection), the MIC score of the AR-NG would decrease the efficacy probability by 25%, 50%, and 100% for a MIC of 2, 3, and 4 respectively (assumed values).

Individuals who were exposed to antibiotic treatment would be partly "protected" from reinfection with CT until the elimination time of azithromycin (15 days [88, 89]) or doxycycline (4 days [90]), and with azithromycin-susceptible NG until the elimination time of azithromycin (15 days [88, 89]) or ceftriaxone (2 days [91]) from the human body. In those cases, the transmission probabilities would be decreased by 50% (assumed). Reinfection with an AR-NG could occur not earlier than 2 days after dual treatment, due to the presence of ceftriaxone in the body.

Simulation and Calibration

The model simulated a population of 10 000 MSM in Belgium over a period of 10 years in daily time steps. Parameters for transmission probabilities, symptomatic infection, duration until natural clearance, probability of abstinence in case of infection, and probabilities for spontaneous azithromycin resistance emergence and horizontal gene transfer were not available in the data sources. Approximate Bayesian

computation with sequential Monte Carlo sampling [92–95] was used to estimate the parameters that were not available. The expected mean CT and NG prevalence in the general MSM population (both groups pooled) at the end of 10 years was used as a target statistic (7% and 0.6% for pharyngeal, 1.5% and 2.9% for urethral, and 9.3% and 8.5% for rectal NG and CT, respectively) [67]. The annual prevalence of azithromycin resistance in NG in the Belgian antimicrobial resistance surveillance reports [21] was also used as a target statistic.

We examined four scenarios (of 100 simulations each) with different treatment options: (1) azithromycin and ceftriaxone (dual therapy) for NG and azithromycin or doxycycline for CT, (2) ceftriaxone monotherapy for NG and azithromycin or doxycycline for CT, (3) dual-therapy for NG and doxycycline for CT, and (4) ceftriaxone monotherapy for NG, doxycycline for CT.

Scenarios 1 and 2 compare mono- and dual therapy in the setting when both azithromycin and doxycycline were used for the treatment of CT, as was the case in Belgium and much of Europe until recently. Scenarios 3 and 4 were chosen to compare mono- and dual therapy in the setting where CT is treated with doxycycline, as recommended in the new European International Union Against STIs guidelines for CT [96]. Results are expressed as means and 95% CIs. Proportions among scenarios were compared using the chi-squared test.

RESULTS

Scenario 1: In the scenario with dual therapy, we were able to reproduce the observed prevalence of NG and CT in Belgium as well as azithromycin resistance in NG in Belgium during 2014–2023 (Figure 1). The 95% CI captures the vast majority of the observed points and follows the general trend of the observed prevalence. Horizontal gene transfer (shown as the red line in Figure 1), was responsible for the majority of AR-NG cases (74.8%).

Scenario 2: In the scenario where ceftriaxone monotherapy is used against NG, and the treatment of CT is unchanged (Figures 2 and 3, Table 1), we observed significant decreases both in NG prevalence as well as in AR-NG prevalence (P values .01 and < .001, respectively), while the CT prevalence increased ($P < .001$). More specifically, the peak prevalence of AR-NG (.23; 95% CI, 0.15–0.31) was approximately half of that in the dual-therapy scenario (0.44; 95% CI, 0.34–0.53).

Scenarios 3 and 4: The prevalence of NG in all 3 sites was slightly higher in scenarios 3 and 4 (Figure 2), where only doxycycline is used for CT treatment, compared to scenario 1 ($P = .269$). For scenario 3, the mean prevalence of CT was similar to scenario 1 ($P = .13$) (Figure 3).

Commensal *Neisseria* and antibiotic consumption: There was little change in the prevalence of azithromycin-resistant traits in CN species between baseline and scenario 3, but this decreased from 44% to 27% when using ceftriaxone monotherapy for NG (scenarios 1 and 2, respectively; $P < .001$) (Table 1). The cumulative consumption of antibiotics in daily defined doses (DDD) decreased for azithromycin between baseline and scenario 2 ($P < .001$) but was unchanged for ceftriaxone ($P = .34$) and increased for doxycycline ($P < .001$). Between baseline and scenario 3, azithromycin and doxycycline consumption increased (P values .025 and < .001, respectively), but ceftriaxone remained at similar levels ($P = .47$). In scenario 4, the consumption of doxycycline increased by 5.4-fold compared to baselines ($P < .001$).

DISCUSSION

Our model was able to replicate the increase in gonococcal resistance to azithromycin among MSM in Belgium over a 10-year span. Moreover, our model examined the effect of different treatment strategies for CT and NG on the prevalence of these infections, the emergence of AR-NG and cumulative antibiotic consumption. Transitioning to ceftriaxone monotherapy resulted in decreasing the prevalence of AR-NG by almost half, while also decreasing the overall NG prevalence. This is an intriguing finding that could be explained by the higher prevalence of NG with azithromycin resistance in the dual-therapy scenario (scenario 1). This increase in azithromycin resistance was, in turn, likely caused by the 3 times higher azithromycin consumption in scenario 1 compared to scenario 2 (464 DDD and 137 DDD, respectively). Azithromycin resistance in NG would provide at least 2 fitness advantages. First, it would be able to survive azithromycin given for an isolated CT (or other infection). Second, it would be able to infect individuals who were exposed to azithromycin in the past 15 days. The higher prevalence of AR-NG in the dual- than the monotherapy scenario would have abrogated these fitness advantages in the dual-therapy arm, thus contributing to an increased gonococcal prevalence over 10 years. An unexpected finding in scenario 3, where azithromycin is used for dual therapy for NG but not for CT treatment, is the higher prevalence of AR-NG than scenario 1. This is likely due to the increased consumption of azithromycin in this scenario, which is in turn due to the fact that the azithromycin used for CT treatment protects against NG infections. Thus, switching to doxycycline treatment for CT means less protection from CT-associated azithromycin use, which in turn results in a higher NG prevalence and the highest azithromycin consumption in scenario 3.

Our results are compatible with the theory that CN species contribute to the emergence of gonococcal antimicrobial resistance. In our model, we found that 74.8% of the AR-NG cases emerged through horizontal gene transfer from CN species. This is considerably higher than the approximately 10%–20% of isolates in Germany and Euro-GASP in 2018 that have

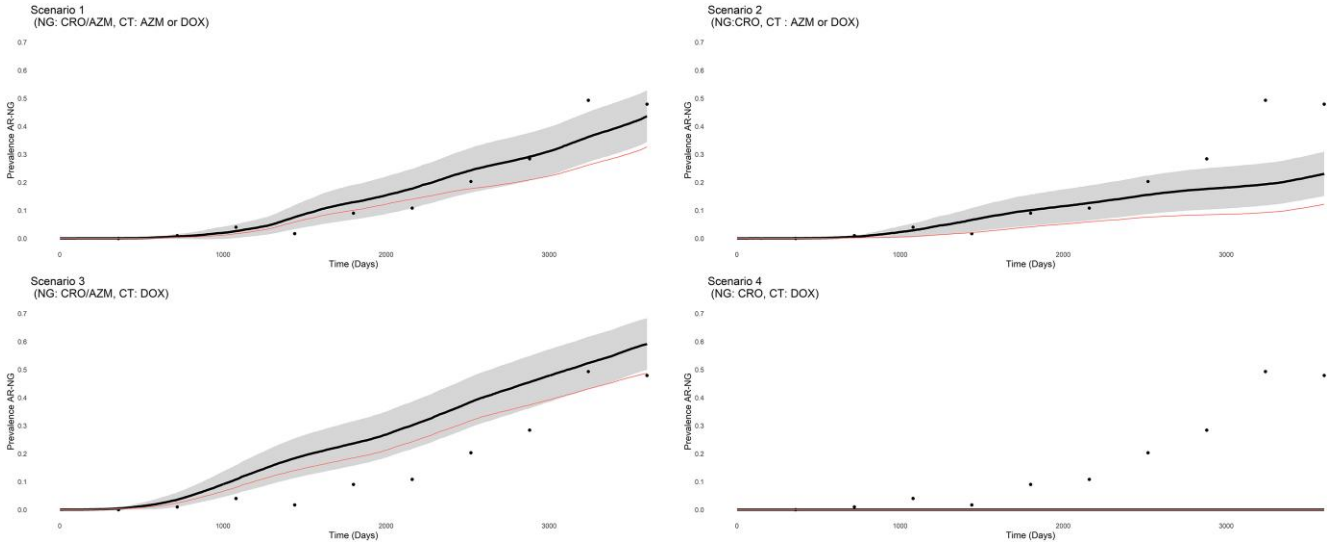

Figure 1. Mean prevalence and 95% CI of azithromycin-resistant NG (AR-NG), over a 10-year period starting in 2014 in 4 scenarios (1) NG: CRO/AZM, CT:AZM, or DOX; (2) NG:CRO, CT:AZM, or DOX, (3) NG:CRO/AZM, CT:DOX; and (4) NG:CRO, CT:DOX. Observed AR-NG from Belgium in the period 2014–2023 are presented as dots. The estimated proportion of AR-NG attributed to horizontal-gene transfer from commensal Neisseria is shown as a red line. Abbreviations: AZM, azithromycin; CI, confidence interval; CRO, ceftriaxone; DOX, doxycycline.

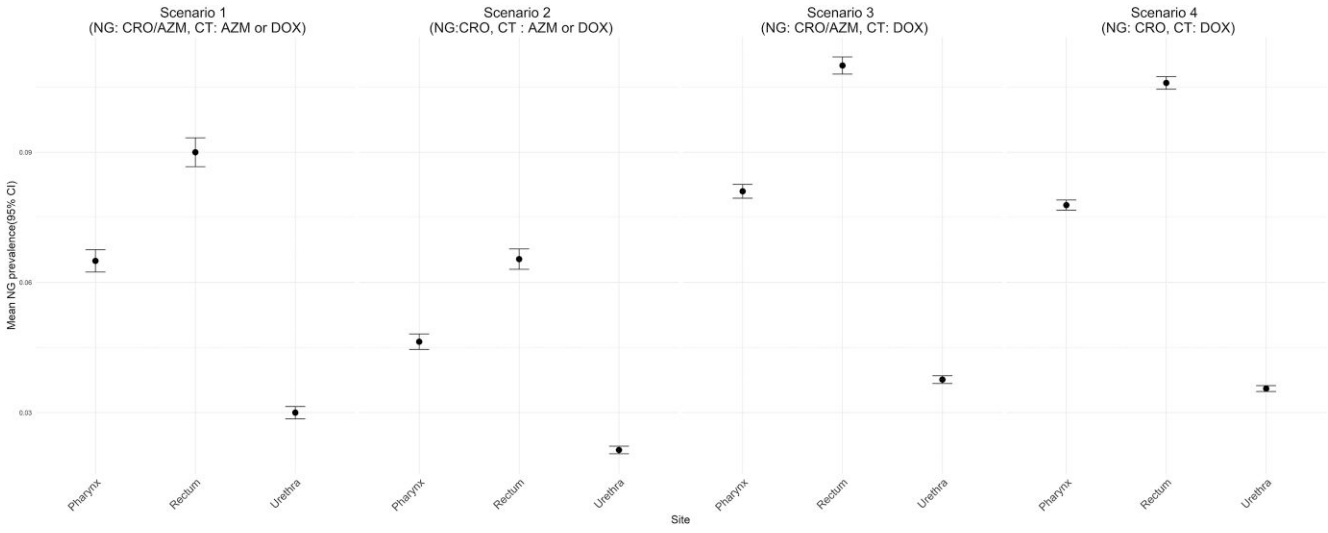

Figure 2. Mean prevalence and 95% CI of *Neisseria gonorrhoeae* by anatomical site at the end of the simulation time. Abbreviations: AZM, azithromycin; CI, confidence interval; CRO, ceftriaxone; DOX, doxycycline.

macrolide resistance via acquisition of a mosaic *mtrCDE* gene [84, 97]. The genetic mechanisms responsible for gonococcal resistance to macrolides are complex and our model is best understood as a first attempt to include the role of horizontal gene transfer from commensals. This aspect of our model is likely to be of greatest utility when modeling extended spectrum cephalosporin resistance, where horizontal gene transfer is responsible for most cases of resistance [98].

Our results are particularly relevant in settings where dual therapy for NG is still favored. A number of countries such as the United States, France, the United Kingdom, and Belgium (in 2023) have changed their national gonococcal treatment guidelines to recommend ceftriaxone monotherapy as the preferred treatment of NG [99, 100]. The European International Union Against STIs has recently changed its guidelines to include ceftriaxone monotherapy as an alternative first-line therapy if 4 preconditions are met [15]. These

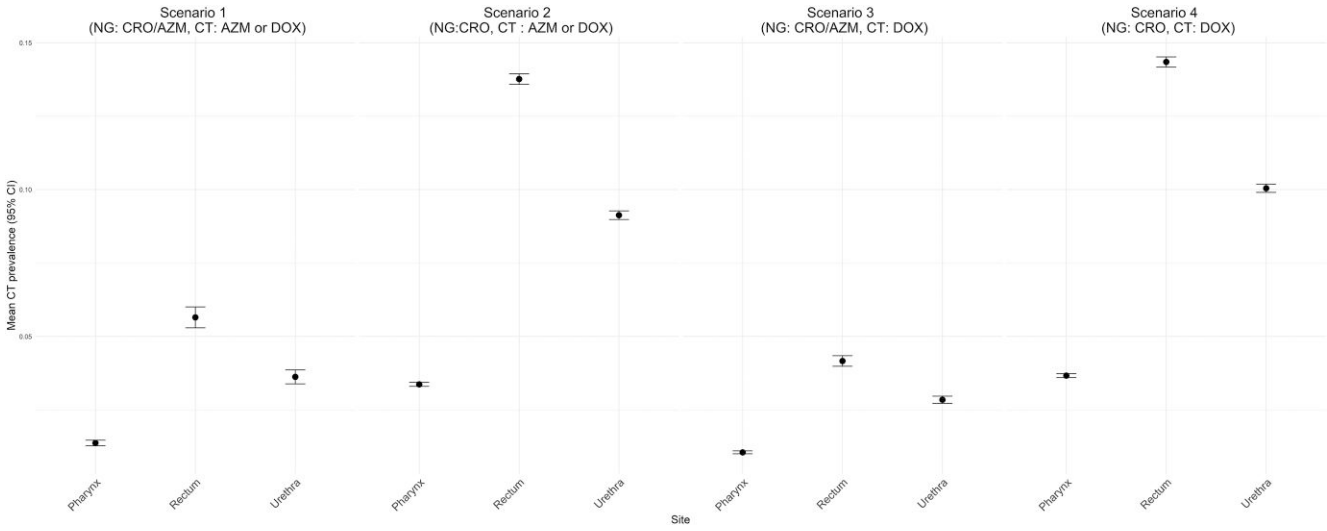

Figure 3. Mean prevalence and 95% CI of *Chlamydia trachomatis* by anatomical site at the end of the simulation time. Abbreviations: AZM, azithromycin; CI, confidence interval; CRO, ceftriaxone; DOX, doxycycline.

Table 1. Mean Estimates With 95% CI at the End of the 10-year Simulation for the 4 Scenarios

	Scenario 1: (NG: CRO/AZM, CT:AZM, or DOX)	Scenario 2: (NG: CRO, CT:AZM, or DOX)	Scenario 3: (NG: CRO/AZM, CT: DOX)	Scenario 4: (NG:CRO, CT:DOX)
Neisseria gonorrhoeae prevalence	0.14 (0.13–0.14)	0.1 (0.1–0.1)	0.16 (0.16–0.17)	0.16 (0.16–0.16)
Chlamydia trachomatis prevalence	0.09 (0.08–0.09)	0.2 (0.2–0.2)	0.07 (0.06–0.07)	0.21 (0.21–0.21)
Cumulative azithromycin consumption (DDD)	464.23 (447.87–480.6)	136.9 (131.88–141.92)	502.4 (487.25- 517.55)	0 (0–0)
Cumulative ceftriaxone consumption (DDD)	31.03 (29.62–32.44)	22.82 (21.75–23.88)	37.68 (36.54–38.82)	35.42 (34.56–36.29)
Cumulative doxycycline consumption (DDD)	170.76 (158.7–182.82)	379.04 (369.41–388.67)	307.74 (294.46–321.02)	925.26 (908.67–941.85)
Azithromycin-resistance commensal *Neisseria* species	0.44 (0.43–0.45)	0.27 (0.26–0.28)	0.43 (0.42–0.44)	0 (0–0)
By anatomical site	…	…	…	…
Pharyngeal *Neisseria gonorrhoeae* prevalence	0.06 (0.06–0.07)	0.05 (0.04–0.05)	0.08 (0.08–0.08)	0.08 (0.08–0.08)
Anorectal *Neisseria gonorrhoeae* prevalence	0.09 (0.09–0.09)	0.07 (0.06–0.07)	0.11 (0.11–0.11)	0.11 (0.1–0.11)
Urethral *Neisseria gonorrhoeae* prevalence	0.03 (0.03–0.03)	0.02 (0.02–0.02)	0.04 (0.04–0.04)	0.04 (0.03–0.04)
Pharyngeal *Chlamydia trachomatis* prevalence	0.01 (0.01–0.01)	0.03 (0.03–0.03)	0.01 (0.01–0.01)	0.04 (0.04–0.04)
Anorectal *Chlamydia trachomatis* prevalence	0.06 (0.05–0.06)	0.14 (0.14–0.14)	0.04 (0.04–0.04)	0.14 (0.14–0.15)
Urethral *Chlamydia trachomatis* prevalence	0.04 (0.03–0.04)	0.09 (0.09–0.09)	0.03 (0.03–0.03)	0.1 (0.1–0.1)
By risk group	…	…	…	…
Neisseria gonorrhoeae prevalence (HA-MSM)	0.26 (0.25–0.27)	0.2 (0.19–0.2)	0.31 (0.31–0.32)	0.3 (0.3–0.31)
Neisseria gonorrhoeae prevalence (LA-MSM)	0.09 (0.08–0.09)	0.06 (0.06–0.07)	0.11 (0.1–0.11)	0.1 (0.1–0.11)
Chlamydia trachomatis prevalence (HA-MSM)	0.18 (0.17–0.19)	0.38 (0.37–0.38)	0.14 (0.13–0.15)	0.4 (0.4–0.4)
Chlamydia trachomatis prevalence (LA-MSM)	0.05 (0.05–0.06)	0.13 (0.13–0.13)	0.04 (0.04–0.04)	0.14 (0.13–0.14)

Abbreviations: AZM, azithromycin; CI, confidence interval; CRO, ceftriaxone; CT, *Chlamydia trachomatis*; DDD, daily defined doses; DOX, doxycycline; HA-MSM, high-activity men having sex with men; LA-MSM, low-activity men having sex with men; NG, *Neisseria gonorrhoeae*.

guidelines thus continue to favor dual therapy. Our results provide additional evidence in favor of switching to monotherapy.

Our model has a number of limitations. First, treatment was assumed to be uniform across all 3 anatomical sites of infection, disregarding poorer azithromycin penetration into the oropharynx, which could lower the treatment efficacy against NG [101]. Second, we assumed that all treatment options for CT/NG infections would be equally chosen regardless of the infected site or a CT/NG co-infection. This assumption deviates from the Belgian treatment guidelines that recommend doxycycline for rectal CT infections [77, 100]. Third, we lacked accurate estimates of a number of the model parameters such as transmission probabilities, duration of infection, and screening rates. We did not explicitly include an incubation period of NG in the model; however, a delay of 5 days between infection and the diagnosis of NG was specified to account for the incubation period and diagnostic delays. The model did not take into account any possible interaction between the 2 STIs of interest or other STIs that could affect the transmission probabilities [102, 103]. We did not include the effect of doxycycline postexposure prophylaxis in the model, which could affect both the calibration process and the final prevalence estimates. Even though doxycycline postexposure prophylaxis is only recommended in research settings in Belgium [104], approximately 10% of MSM have reported using it to prevent STIs [105]. Our model does not include the age of individuals or any temporal changes, either in the consistency of the population (entries or exits from the network) or in the behavioral characteristics of individuals (people cannot change risk-group over time). Last, the effect of important factors, such as transmission of either infection or of commensal species through kissing (pharynx to pharynx) and the antibiotic consumption for non-STI reasons were not included in the model. Transmission of both chlamydia and gonorrhea through kissing has been documented in several clinical and modeling studies [106–112]. Additionally, there is increasing evidence that bystander selection (the selection pressure for resistance through the use of antibiotics for other indications) plays an important role in the genesis of AMR [113–115]. In fact, in 2023, it was reported that 541 DDD of cephalosporines, 1588 DDD of macrolides, and 656 DDD tetracyclines were used in Belgium for any reason [116]. Omission of these factors could affect the calibration of the transmission probabilities and/or the effect of different treatment options compared to scenario 1.

Despite the many limitations, our study also has significant strengths, as it attempts to explain the complex mechanisms of NG transmission and AMR emergence in a highly detailed network model that incorporates commensal bacteria. Previously published models either used a compartmental approach did not include NG from all 3 anatomical sites, did not include commensal *Neisseria* spp., or did not include antibiotic use for CT [24, 25, 36, 53–55]. Future NG AMR models would benefit from including antibiotics used for other indications as well as more accurate behavioral and transmission parameters.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. C.K., N.H., C.v.D., and A.T. conceived and designed the study. A.T. curated the data and A.T. and C.v.D. contributed in model development. A.T. and C.K. wrote the original draft. C.K., N.H., C.v.D., and A.T. critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Ethical considerations. The parameters in this study are derived from already published papers. In the case of primary data from the PreGo and Gonoscreen studies, written informed consents were obtained for all participants. The PreGo study obtained an ethics approval from the Institutional Review Board of the Institute of Tropical Medicine (1276/18) and from the Ethics Committee of the University of Antwerp (19/06/058). The Gonoscreen study obtained an ethics approval from the Institutional Review Board of the Institute of Tropical Medicine (1360/20).

Financial support. The Gonoscreen study was funded by the Belgian Health Care Knowledge Center (KCE, INV 18-1133) C.V.D. received funding from the Fonds Wetenschappelijk Onderzoek (FWO grant number 12B1M24N).

Potential conflicts of interest. All authors declare that they have no conflicts of interest.

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