Published in final edited form as:

Sex Transm Dis. 2023 May 01; 50(5): 317–319. doi:10.1097/OLQ.0000000000001769.

Predominance of high-level tetracycline-resistant *Neisseria gonorrhoeae* in Kenya: Implications for global implementation of doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections

Olusegun O. Soge, MSc, PhD[1,2,3], **Rodal Issema, MPH**[4], **Elizabeth Bukusi, MPH, PhD**[1,5,6], **Jared M. Baeten, MD, PhD**[1], **Andrew Mujugira, MBChB, PhD**[1,7], **Connie Celum, MD, MPH**[1,2,4], **R. Scott McClelland, MD, MPH**[1,2,4], **Jenell Stewart, DO, MPH**[8,9], **Partners PrEP Study Team**

[1]Department of Global Health, University of Washington, Seattle, WA

[2]Department of Medicine, University of Washington, Seattle, WA

[3]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA

[4]Department of Epidemiology, University of Washington, Seattle, WA

[5]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA

[6]Kenya Medical Research Institute (KEMRI), Nairobi, Kenya

[7]Infectious Diseases Institute, Makerere University, Kampala, Uganda

[8]Hennepin Healthcare Research Institute, Minneapolis, MN

[9]Department of Medicine, University of Minnesota, Minneapolis, MN

Abstract

Using archived *Neisseria gonorrhoeae* samples from 2008–2012, the prevalence of *tet*(M) gene mediating high-level tetracycline resistance in *N. gonorrhoeae* was 96% among 50 Kenyan women. Determining local and national prevalence of gonococcal tetracycline resistance and surveillance of gonococcal antimicrobial resistance can inform implementation of doxycycline post-exposure prophylaxis for STI prevention.

Short Summary

Most archived *Neisseria gonorrhoeae* samples collected from 2008–2012 from Kenyan women had *tet*(M)-encoding high-level tetracycline resistance; this could reduce the efficacy of doxycycline post-exposure prophylaxis against *N. gonorrhoeae*.

Corresponding Author: Olusegun O. Soge, MSc, PhD, University of Washington, Harborview Medical Center, 325 9th Avenue Box 359931, Seattle, WA 98104, Phone: (206) 897-5325, Fax: (206) 897-5304, sogeo@uw.edu.

Conflicts of interest

Dr. Soge has received research funding outside the submitted work, awarded to the University of Washington, from Hologic Inc. and SpeeDx. Dr. Baeten is an employee of Gilead Sciences outside of the submitted work. Dr. McClelland has received honoraria for consulting for Lupin Pharmaceuticals and research funding, paid to the University of Washington, from Hologic Corporation. All other co-authors do not have any declared conflict of interest.

Keywords

Neisseria gonorrheoae antimicrobial resistance; high-level tetracycline resistance; doxycycline post-exposure prophylaxis; STIs; gonorrhea

Introduction

Neisseria gonorrhoeae (NG) infection is the second most common bacterial sexually transmitted infection (STI) in the world, and it is associated with substantial morbidity and economic cost [1,2]. The World Health Organization (WHO) estimates that in 2020, 82.4 million new cases of NG occurred among adolescents and adults [1]. STIs, including NG infection, are often under-reported in many African countries, in part because syndromic management is used much more commonly than diagnostic testing in symptomatic individuals and screening is rarely available for persons who are asymptomatic [3]. Data from HIV PrEP trials among Eastern and Southern African women indicate high incidence of NG (up to 20 per 100 person-years) [4].

Biomedical interventions for STI prevention such as doxycycline prophylaxis have been proposed to be valuable for reducing the incidence of bacterial STIs among users of HIV PrEP, but antibiotic prophylaxis could both select for and be undermined by antimicrobial resistance (AMR).

Two clinical trials have demonstrated that doxycycline post-exposure prophylaxis (doxycycline PEP) reduces the incidences of bacterial STIs, NG, *Chlamydia trachomatis* (CT), and *Treponema pallidum* (TP) by 70% among men who have sex with men (MSM) in France and by 62% among both MSM and transgender women in the United States [5,6]. However, there are concerns that doxycycline PEP also could induce or promote AMR in STI and non-STI pathogens and commensal bacteria [7]. Antimicrobial-resistant NG is a public health issue globally, with a growing threat of untreatable multidrug resistant cases [8,9], but there are limited NG resistance data from Africa [10,11]. The community-level prevalence of tetracycline-resistant NG is an important clinical factor that may influence the effectiveness of doxycycline PEP for STI prevention in each setting. In addition, CT is more common than NG [1], and they often occur as co-infections. There are no reported cases of laboratory-confirmed tetracycline resistance in CT, although there is theoretical risk based on rare reports of resistance mediated by the *tet*(C) gene among *Chlamydia suis* in animals [12].

Using archived endocervical swab specimens collected from 2008 and 2012 for STI testing in Kenya [13,14], we evaluated the prevalence of tetracycline-resistant NG and CT among cisgender women prior to launching a study of doxycycline PEP among cisgender women in Kenya [15].

Methods

Between 2008 and 2012, 9,494 participants were enrolled and followed in the Partners PrEP Study, a randomized clinical trial of antiretroviral HIV pre-exposure prophylaxis

(PrEP) among heterosexual HIV serodifferent couples, at nine sites in Kenya and Uganda [13,14]. The study protocol was approved by the University of Washington (UW) Human Subjects Review Committee and ethics review committees at each of the study sites, and all participants provided written informed consent in English or their primary language [13,14]. Endocervical swabs were collected from HIV seropositive female participants every 12 months for NG and CT testing by nucleic acid amplification test (NAAT) and duplicate endocervical swabs were stored at −80C at the UW for future STI research. All participants with an STI received treatment according to the national STI treatment guidelines. The laboratory work described in this paper was performed at the UW Neisseria Reference Laboratory. The DNA from 50 randomly selected swabs collected from heterogenous population from 4 sites in Kenya (Eldoret, Kisumu, Nairobi, and Thika) from visits at which NG had been detected by NAAT was purified and extracted (supplementary Table S1). DNA samples were used as templates for detection of the *tet*(M) genes of the American and Dutch plasmids using previously described PCR and cycling parameters, and standard positive and negative controls [16, 17]. Additionally, the DNA from 10 randomly-selected endocervical swabs, which had tested positive for CT by NAAT with no concurrent NG detected, were tested for *tet*(C) gene [12]. Descriptive data analyses were performed with Stata version 15.0 software (StataCorp).

Results

A total of 9,494 participants, including 4,747 cisgender women, were enrolled in the Partners PrEP Study, with a median age of 33 years. Among participants living with HIV (n=4,712), the prevalence of NG was 1.4% and CT 0.6%; NG incidence during follow-up was 4.9 per 100 person-years and CT 1.1 per 100 person-years. At enrollment, 9,415 participants were tested for STIs with 683 participants found to be positive (*Trichomonas vaginalis*, CT, and/or NG).

Of the fifty archived endocervical swabs with NG detected by NAAT, 48 (96%) carried the American type plasmid-mediated *tet*(M) gene conferring high-level tetracycline resistance. None of the 50 endocervical swabs harbored the Dutch type *tet*(M). Sixteen (32%) participants received treatment as syndromic management or directed treatment for a documented STI prior to swab collection; however, there was no doxycycline given to participants prior to collection of swabs tested for *tet*(M) [Table 1]. Prophylactic use of trimethoprim-sulfamethoxazole as part of HIV care to reduce bacterial infections was common among the 49 participants, and 7 (14%) had a prior diagnosis of pelvic inflammatory disease [Table 1]. None of the 10 additional endocervical swabs with CT tested positive for *tet*(C).

Discussion

We observed a high prevalence of high-level tetracycline resistance mediated by the American variant *tet*(M) gene among non-cultured NG samples from 50 Kenyan women. Therefore, doxycycline PEP for STI prevention may have limited efficacy against gonorrhea in sub-Saharan Africa, although use of doxycycline is also unlikely to select for additional resistance to tetracyclines in NG given the near-universal prevalence of *tet*(M). The

impact of trimethoprim-sulfamethoxazole prophylaxis among persons with advanced HIV immunosuppression on cross-resistance selection to other categories of antibiotics such as tetracyclines is yet to be fully elucidated. We did not detect the *tet*(C) from the CT samples confirming no hypothetical resistance, which is consistent with results to date worldwide [12].

Recently, analyses of whole genome sequence (WGS) data have shown that high percentages (86–97%) of NG isolates collected in Kenya between 2010 and 2018 carried the plasmid-mediated tetracycline resistance *tet*(M) gene [10,18]. Moreover, high percentages of carriage of the plasmid-mediated *tet*(M) gene, conferring high-level tetracycline resistance determined by PCR and/or by antimicrobial susceptibility testing, have been reported from cultured NG isolates from other sub-Saharan African countries including South Africa, 2008–2012 (73–92%) [19, 20], Mozambique, 2005 (77%) [21], and Uganda, 2008–2009 (90%, TET MIC_{90} 16μg/mL) [22]. Consistent with our finding of the American variant *tet*(M) gene from all 48 non-cultured NG samples, a previous study from South Africa found all 136 NG isolates with high-level tetracycline resistance (MIC≥16μg/mL) to carry the American variant of the tet(M) gene [23], and a recent study from Kenya found that 30 (97%) of 31 NG *tet*(M)-encoding plasmids were American type [18]. Epidemic spread of plasmid-mediated tetracycline-resistant NG has been previously reported in sex workers in Kinshasa, Zaire [24], and gonorrhea treatment failures have been associated with high-level tetracycline resistant NG strains [25]. Of note, data from Africa are in contrast to those from the United States, where circulating plasmid-mediated tetracycline resistant NG are not universal and where recent data revealed NG prevention in a doxycycline PEP trial [6].

We acknowledge the small sample size and the use of endocervical specimens collected approximately 10 years ago. However, our culture-independent molecular approach for detecting plasmid-mediated tetracycline resistance from non-cultured clinical specimens is a strength and has been recommended by WHO for enhancing gonococcal AMR surveillance [26].

Public health and provider messaging about doxycycline PEP efficacy against NG will vary by NG tetracycline resistance rate, which is dynamic in the setting of increasingly interconnected sexual networks; but it could still be efficacious for CT and TP. We recommend that integral components of the implementation of doxycycline PEP for STI prevention should include establishing the local prevalence of NG tetracycline resistance and ongoing robust surveillance of gonococcal antimicrobial resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Source of funding:

This work was funded by The US National Institutes of Health (grants R01AI145971, P30AI027757, K23MH124466, 1R21AI166896)

References

1. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021: actions for impact: web annex 2: data methods Available at https://www.who.int/publications/i/item/9789240027077. Accessed November 5, 2022.
2. Whittles LK, Didelot X, White PJ. Public health impact and cost-effectiveness of gonorrhoea vaccination: an integrated transmission-dynamic health-economic modelling analysis. Lancet Infect Dis 2022; 22(7):1030–1041. [PubMed: 35427491]
3. Otieno FO, Ndivo R, Oswago S, et al. Evaluation of syndromic management of sexually transmitted infections within the Kisumu Incidence Cohort Study. Int J STD AIDS 2014; 25(12):851–859. [PubMed: 24516075]
4. Stewart J, Bukusi E, Celum C, et al. Sexually transmitted infections among African women: an opportunity for combination sexually transmitted infection/HIV prevention. AIDS 2020; 34(5):651–658. [PubMed: 32167988]
5. Molina JM, Charreau I, Chidiac C et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis 2018; 18(3):308–317. [PubMed: 29229440]
6. Luetkemeyer A, Dombrowski J, Cohen S, et al. Doxycycline post-exposure prophylaxis for STI prevention among MSM and transgender women on HIV PrEP or living with HIV: high efficacy to reduce incident STI's in a randomized trial 24th International AIDS Conference; July 29 - August 2; Montreal, Canada, 2022.
7. Kohli M, Medland N, Fifer H, et al. BASHH updated position statement on doxycycline as prophylaxis for sexually transmitted infections. Sex Transm Infect 2022; 98(3):235–236. [PubMed: 35414633]
8. Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. Future Microbiol 2012; 7(12):1401–1422. [PubMed: 23231489]
9. Fifer H, Natarajan U, Jones L, et al. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea. N Engl J Med 2016; 374(25):2504–2506. [PubMed: 27332921]
10. Cehovin A, Harrison OB, Lewis SB, et al. Identification of Novel Neisseria gonorrhoeae Lineages Harboring Resistance Plasmids in Coastal Kenya. J Infect Dis 2018; 218(5):801–808. [PubMed: 29701830]
11. Lewis DA, Sriruttan C, Müller EE, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure. J Antimicrob Chemother 2013; 68(6):1267–1270. [PubMed: 23416957]
12. Wanninger S, Donati M, Di Francesco A, et al. Selective Pressure Promotes Tetracycline Resistance of Chlamydia Suis in Fattening Pigs. PLoS One 2016; 11(11):e0166917. [PubMed: 27893834]
13. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012; 367(5):399–410. [PubMed: 22784037]
14. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. Lancet Infect Dis 2014; 14(11):1055–1064. [PubMed: 25300863]
15. Stewart J, Bukusi E, Sesay FA, et al. Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis: study protocol for an open-label randomized trial. Trials 2022; 23(1):495. [PubMed: 35710444]
16. Pitt R, Sadouki Z, Town K, et al. Detection of tet(M) in high-level tetracycline-resistant Neisseria gonorrhoeae. J Antimicrob Chemother 2019; 74(7):2115–2116. [PubMed: 31225605]
17. Turner A, Gough KR, Leeming JP. Molecular epidemiology of tetM genes in Neisseria gonorrhoeae. Sex Transm Infect 1999;75(1):60–66. [PubMed: 10448346]

18. Kivata MW, Mbuchi M, Eyase F, et al. Plasmid mediated penicillin and tetracycline resistance among Neisseria gonorrhoeae isolates from Kenya. BMC Infect Dis 2020 Sep 25;20(1):703. [PubMed: 32977759]

19. Fayemiwo SA, Müller EE, Gumede L, et al. Plasmid-mediated penicillin and tetracycline resistance among Neisseria gonorrhoeae isolates in South Africa: prevalence, detection and typing using a novel molecular assay. Sex Transm Dis 2011 Apr;38(4):329–33. [PubMed: 21042234]

20. Rambaran S, Naidoo K, Dookie N, et al. Resistance Profile of Neisseria gonorrhoeae in KwaZulu-Natal, South Africa Questioning the Effect of the Currently Advocated Dual Therapy. Sex Transm Dis 2019; 46(4):266–270. [PubMed: 30657464]

21. Apalata T, Zimba TF, Sturm WA, et al. Antimicrobial susceptibility profile of Neisseria gonorrhoeae isolated from patients attending a STD facility in Maputo, Mozambique. Sex Transm Dis 2009; 36(6):341–343. [PubMed: 19556927]

22. Vandepitte J, Hughes P, Matovu G, et al. High prevalence of ciprofloxacin-resistant gonorrhea among female sex workers in Kampala, Uganda (2008–2009). Sex Transm Dis 2014; 41(4):233–237. [PubMed: 24622633]

23. Moodley P, Hoppenbrouwers J, Bohlken L et al. Emergence of TetM-mediated tetracycline resistance in rural South Africa. J Antimicrob Chemother 2001; 48: 142–143. [PubMed: 11418527]

24. Van Dyck E, Laga M, Manoka AT, et al. Epidemic spread of plasmid-mediated tetracycline resistant Neisseria gonorrhoeae in Zaire. Int J STD AIDS 1995; 6(5):345–7. [PubMed: 8547415]

25. Centers for Disease Control (CDC). Plasmid-mediated tetracycline-resistant Neisseria gonorrhoeae--Georgia, Massachusetts, Oregon. MMWR Morb Mortal Wkly Rep 1986; 35(19):304–306. [PubMed: 3084943]

26. World Health Organization. Global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae Available at https://apps.who.int/iris/handle/10665/44863. Accessed November 5, 2022.

Table 1.

Recent antibiotic exposures and risk factors for tetracycline antimicrobial resistance among 50 female participants in Kenya found to have *N. gonorrhoeae infection* in the Partners PrEP Study, 2008–2012

Characteristics	*tet*(M) Negative N = 2	*tet*(M) Positive N = 48*
Prior diagnosis of vaginal discharge	1 (50%)	11 (23%)
Prior diagnosis of Cervicitis	2 (100%)	3 (6.3%)
Prior diagnosis of Pelvic Inflammatory Disease	2 (100%)	5 (10%)
Prior diagnosis of Neisseria gonorrhoeae	0 (0%)	14 (29%)
Prior diagnosis of Chlamydia trachomatis	0 (0%)	1 (2.1%)
Taking prophylactic trimethoprim-sulfamethoxazole	2 (100%)	47 (98%)
Recent treatment with doxycycline (<1 month)	0 (0%)	0 (0%)

*All 48 *tet*(M) Positive samples were American variant of the *tet*(M) gene

Sex Transm Dis. Author manuscript; available in PMC 2024 May 01.