High tetracycline resistance percentages in *Neisseria gonorrhoeae* in Europe: is doxycycline post-exposure prophylaxis unlikely to reduce the incident gonorrhoea cases?

Magnus Unemo,[a,b,*] Michelle J. Cole,[c] Csaba Kodmon,[d] Michaela Day,[c] and Susanne Jacobsson,[a] the European Gonococcal Tetracycline-Resistance Study Group

[a]WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for STIs, Department of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
[b]Institute for Global Health, University College London (UCL), London, UK
[c]UK Health Security Agency (UKHSA), London, UK
[d]European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

The Lancet Regional Health - Europe 2024;38: 100871
Published Online 13 February 2024
https://doi.org/10.1016/j.lanepe.2024.100871

Sexually transmitted infections (STIs) remain global public health concerns, and novel interventions to decrease their incidence are essential. In two randomised clinical studies, doxycycline post-exposure prophylaxis (doxycycline-PEP) significantly reduced the incident bacterial STIs in USA[1] and France.[2] Doxycycline 200 mg was taken, by mostly men-who-have-sex-with-men (MSM) using HIV Pre-Exposure Prophylaxis (PrEP) or living with HIV and who had ≥1 bacterial STI in the past year, ideally within 24 h (no later than 72 h) after condomless sex.[1,2] The incident chlamydial, syphilis and gonorrhoea cases significantly decreased in USA,[1] while only chlamydial and syphilis cases significantly decreased in France.[2] The limited effect on gonorrhoea in France, compared to USA, was likely due to a higher resistance to doxycycline/tetracycline (tetracycline testing reflects the susceptibility to tetracyclines including doxycycline) in *Neisseria gonorrhoeae*. Gonococcal tetracycline susceptibility was not surveyed in the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) in the recent decade, since tetracyclines have not been a gonorrhoea treatment option for decades. However, the European Centre for Disease Prevention and Control (ECDC), and many other public health organisations, now consider formulating evidence-based recommendations regarding doxycycline-PEP as a public health intervention,[3] and gonococcal tetracycline resistance data in Europe, and globally, are imperative.

Herein, we present tetracycline resistance data for gonococcal isolates (n = 4787) from 19 EU/EEA countries in 2022 (Table 1), i.e., to estimate doxycycline-PEP effectiveness in reducing gonorrhoea cases in Europe.

The tetracycline MIC range, MIC_{50} (range), MIC_{90} (range) and resistance percentage (range) using the clinical tetracycline resistance breakpoint (MIC > 0.5 mg/L) stated by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (v14.0; https://www.eucast.org/clinical_breakpoints) in the 19 EU/EEA countries was 0.032–>256 mg/L, 1 (0.25–2) mg/L, 16 (1–64) mg/L, and 63.4% (14.3–93.7%), respectively. Of the 19 countries, 84.2% (16/19) showed >30%, 57.9% (11/19) >50%, and 36.8% (7/19) >70% resistance to tetracycline, respectively (Table 1). For comparison, using the EUCAST breakpoint, the tetracycline resistance percentage in England and Wales in 2022 (https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report/grasp-report-data-to-june-2023) and in USA in 2021 (https://www.cdc.gov/std/statistics/gisp-profiles/default.htm) were 84.1% (1228/1460) and 67.5% (2580/3823), respectively. Furthermore, in many African countries, based on molecular resistance determinants, high-level plasmid (*tetM*)-mediated tetracycline resistance is >90%.[4]

Accordingly, the overall gonococcal tetracycline resistance in Europe and internationally is high, thus questioning whether doxycycline-PEP would considerably decrease gonorrhoea incidence across Europe and in many global settings. The tetracycline resistance in France was 92.3%, which could partly explain the lack of doxycycline-PEP effect on gonorrhoea in the French study.[2] However, the EUCAST clinical tetracycline resistance breakpoint is for gonorrhoea treatment, and it remains unknown whether this breakpoint appropriately reflects resistance to doxycycline-PEP, i.e., taking doxycycline 200 mg within ideally 24 h as PEP instead of treating more established gonococcal infections. Notably, using the clinical tetracycline resistance breakpoint stated by the US Clinical and Laboratory Standards Institute (MIC > 1.0 mg/L; www.clsi.org), resistance breakpoint for minocycline (another tetracycline) when minocycline 200 mg was taken for PEP after sexual intercourse (MIC > 2 mg/L),[5] and breakpoint for high-level plasmid (*tetM*)-mediated tetracycline

*Corresponding author.
E-mail address: magnus.unemo@regionorebrolan.se (M. Unemo).

resistance (MIC > 8 mg/L), the mean tetracycline resistance in Europe was 38.6% (Table 1), 19.7%, and 13.3%, respectively.

In conclusion, the high gonococcal tetracycline resistance in Europe questions the impact of doxycycline-PEP against gonorrhoea in Europe. Although a reduction in gonorrhoea may be observed in countries with lower resistance percentages and more low-level resistance (based on tetracycline MICs), doxycycline-PEP could subsequently rapidly select for gonococcal strains with tetracycline resistance (low-level and high-level) and also multidrug-resistance. Many long-term effects on STI prevalence, microbiomes, and selection of antimicrobial resistance in STIs, non-STI pathogens, and commensals, also remain unknown.[3,6] Nevertheless, doxycycline-PEP is effective, in the short term, at reducing incident chlamydial and syphilis cases in MSM with frequent bacterial STIs.[1,2] Doxycycline-PEP is also already used in the MSM community (prescribed or obtained online).[3,6] Dissemination of current evidence regarding positive effects and unknowns concerning long-term effects of doxycycline-PEP to community and medical staff and medical supervision of doxycycline-PEP use restricted to STI high-risk populations (and restricted to only doxycycline) with regular STI testing and counselling are imperative. Finally, phenotypic and genomic monitoring (especially from doxycycline breakthrough STIs) of STI and non-STI pathogens are crucial.[3,6]

European gonococcal tetracycline-resistance study group

Eszter Balla, Beatrice Bercot, Maria José Borrego, Dominique Caugant, Michelle Cole, Brendan Crowley, Michaela Day, Irith De Baetselier, Dagmar Heuer, Susanne Jacobsson, Csaba Kodmon, Vivi Miriagou, Beata Młynarczyk-Bonikowska, Peter Pavlik, Ivva Philipova, Stefanie Schindler, Daniel Schröder, Raquel Abad Torreblanca, Kairi Tõnsau, Magnus Unemo, Alje Van Dam, Francesca Vella, Polona Maver Vodičar, and Hana Zákoucká.

Contributors

MU, MJC, CK, MD, and SJ designed, initiated, and coordinated the study. The European study group members supplied gonococcal tetracycline susceptibility data from decentralised testing or provided gonococcal isolates for centralised tetracycline susceptibility testing. SJ performed the centralised tetracycline susceptibility testing. SJ and MU analysed and interpreted all the tetracycline susceptibility data. MU wrote a first draft of the paper. MU, MJC, CK, MD, SJ, and the European study group members read, commented on, and approved the final manuscript. The first author (MU) and the last author (SJ) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Most data collected and analysed in this study are included in the paper. However, remaining datasets can be made available from the corresponding author after publication on reasonable request.

Declaration of interests

We declare no competing interest.

Countries (no. of isolates)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	EUCAST-no. of resistant isolates (%)[a]	CLSI-no. of resistant isolates (%)[b]	Tetracycline susceptibility testing method[c]
Austria (n = 379)	0.125–128	1	32	278 (73.4)	178 (47.0)	Decentralised, MGST
Belgium (n = 669)	≤0.125–≥128	1	32	516 (77.1)	253 (37.8)	Decentralised, AD
Bulgaria (n = 12)	0.25–32	1	16	9 (75.0)	2 (16.7)	Centralised, MGST
Czechia (n = 112)	0.125–64	1	32	57 (50.9)	24 (21.4)	Centralised, MGST
Estonia (n = 7)	0.064–16	0.5	16	1 (14.3)	1 (14.3)	Decentralised, MGST
France (n = 220)	0.25–>256	2	32	203 (92.3)	126 (57.3)	Decentralised, MGST
Germany (n = 200)	0.25–256	2	32	173 (86.5)	158 (79.0)	Decentralised, MGST
Greece (n = 100)	0.032–16	0.5	1	33 (33.0)	7 (7.0)	Decentralised, MGST
Hungary (n = 122)	0.125–128	1	16	73 (59.8)	26 (21.3)	Centralised, MGST
Ireland (n = 248)	0.125–32	0.5	1	114 (46.0)	20 (8.1)	Decentralised, MGST
Malta (n = 61)	0.064–32	0.5	8	20 (32.8)	16 (26.2)	Decentralised, MGST
The Netherlands (n = 196)	0.125–64	1	16	128 (65.3)	39 (19.9)	Centralised, MGST
Norway (n = 827)	0.032–64	0.5	16	324 (39.2)	170 (20.6)	Decentralised, MGST
Poland (n = 15)	0.5–16	1	4	8 (53.3)	2 (13.3)	Centralised, MGST
Portugal (n = 841)	0.25–>256	2	64	788 (93.7)	693 (82.4)	Decentralised, MGST
Slovakia (n = 80)	0.125–32	0.5	16	37 (46.3)	19 (23.8)	Centralised, MGST
Slovenia (n = 285)	0.032–32	0.5	1	71 (24.9)	14 (4.9)	Decentralised, MGST
Spain (n = 213)	0.064–32	0.25	2	39 (18.3)	22 (10.3)	Decentralised, MGST
Sweden (n = 200)	0.125–>256	1	32	162 (81.0)	80 (40.0)	Decentralised, MGST
Total = 4787	**0.032–>256**	**1**	**16**	**3034 (63.4%)**	**1850 (38.6%)**	

The bold values are the values for the total number of isolates. No. = number; MIC = minimum inhibitory concentration; MGST = MIC gradient strip test (mostly Etest; bioMérieux, Marcy-Étoile, France); AD = agar dilution method. [a]Based on the clinical tetracycline resistance breakpoint (MIC > 0.5 mg/L) stated by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (v14.0; https://www.eucast.org/clinical_breakpoints). [b]Based on the clinical tetracycline resistance breakpoint (MIC > 1.0 mg/L) stated by the US Clinical and Laboratory Standards Institute (www.clsi.org). [c]Tetracycline MICs (mg/L) were determined by either MIC gradient strip test, according to manufacturer's instructions, or agar dilution.

Table 1: **Tetracycline susceptibility in *Neisseria gonorrhoeae* isolates (n = 4787) cultured in 19 EU/EEA countries in 2022.**

Acknowledgements
We are grateful to Otilia Mårdh for her valuable comments on our paper.

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100871.

References
1 Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *N Engl J Med*. 2023;388:1296–1306.
2 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;18:308–317.
3 Mårdh O, Plachouras D. Using doxycycline for prophylaxis of bacterial sexually transmitted infections: considerations for the European Union and European Economic Area. *Euro Surveill*. 2023;28:2300621.
4 Kakooza F, Golparian D, Matoga M, et al. Genomic surveillance and antimicrobial resistance determinants in *Neisseria gonorrhoeae* isolates from Uganda, Malawi and South Africa, 2015-20. *J Antimicrob Chemother*. 2023;78:1982–1991.
5 Harrison WO, Hooper RR, Wiesner PJ, et al. A trial of minocycline given after exposure to prevent gonorrhea. *N Engl J Med*. 1979;300:1074–1078.
6 Kong FYS, Kenyon C, Unemo M. Important considerations regarding the widespread use of doxycycline chemoprophylaxis against sexually transmitted infections. *J Antimicrob Chemother*. 2023;78:1561–1568.