



Doxycycline PEP – antimicrobial resistance (AMR) considerations

AVAC STI Awareness Week
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Associate Prof. Fabian Kong BPharm, MEpi, PhD

Today

- Of trial results, cure for NG lowest and concerns
- Antimicrobial resistance (AMR)
 - STIs and commensals e.g. *S.aureus*
 - Cross resistance to other antibiotics
- Antibiotic stewardship among users
- Need for ongoing surveillance over longer follow up



Doxycycline pharmacology

- Class: 2nd generation tetracycline
 - Less side effects
 - Greater absorption (~73-95% dose absorbed)
 - More 'fat soluble' – crosses fatty cells walls of human cells
 - Widely distributed in body
- Broad spectrum
 - Gram+ve, Gram–ve, some anaerobes**
 - Spirochetes (syphilis, TP) and parasites (malaria)
- Well tolerated
 - Common (>1%): **nausea, vomit, diarrhoea, epigastric burning,** tooth discolouration and photosensitivity
 - Rare (<0.1%): throat ulcers, hepatitis, benign intracranial hypertension

** Bacteroides fragilis, Clostridium, Fusobacterium, Fusobacterium spp



Effectiveness of doxy PrEP/PEP

- PrEP (n=30) and cis-women: Doxy not effective
- PEP (Ipergay, DoxyPEP, DoxyVAC): 200mg <72h sex
 - MSM/TGW
 - Follow up 35-56 weeks

Incidence reduction

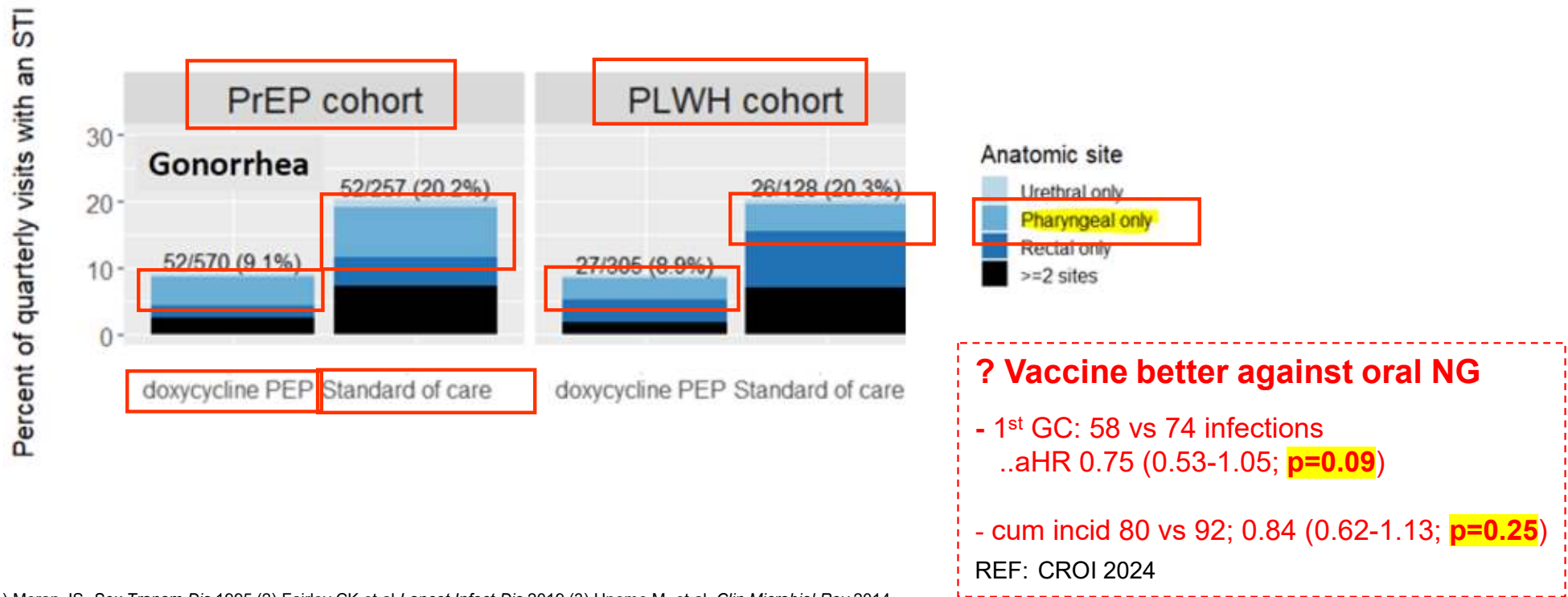
- **Any STI (CT/TP/NG):** ~60% [47-65%]
- **CT/TP:** ~80% [70-86%CT, 73-82% TP]
- **NG:**
 - France
 - Ipergay²⁰¹⁵ 17% (p=0.52) [Tc-R 50-60%²⁰¹²⁻¹⁴]
 - DoxyVAC²⁰²² 33% [Tc-R 65²⁰²¹]
 - USA: 55%²⁰²⁰⁻²² [Tc-R 20-30%]

(1) Bolan RK. STD 2015 DOI: [10.1097/OLQ.0000000000000216](https://doi.org/10.1097/OLQ.0000000000000216) (2) https://www.natap.org/2023/CROI/croi_10.htm (3) Molina J-M. Lancet Infect Dis 2018 DOI: [10.1016/S1473-3099\(17\)30725-9](https://doi.org/10.1016/S1473-3099(17)30725-9)
(4) Luetkemeyer A. NEJM 2023 DOI: [10.1056/NEJMoa2211934](https://doi.org/10.1056/NEJMoa2211934) (5) CROI 2024



DoxyPEP leaves behind NG in the mouth

- NG in mouth
 - Higher **treatment failure** vs genital/rectum
 - MSM: oral NG ↓ ceft. susc (↑Az-R) vs other sites (BASHH2023, GRASP)
 - Major **transmission** via oral sex/saliva
 - Mouth is where **AMR** develops via oral commensals



(1) Moran JS. *Sex Transm Dis* 1995 (2) Fairley CK et al *Lancet Infect Dis* 2019 (3) Unemo M, et al. *Clin Microbiol Rev* 2014



DoxyPEP leaves behind lots of oral NG

Similar in IPERGAY PEP

- trends towards reduction NG at anus/urine but not in throat



N. gonorrhoeae Infections with Doxy



| | PEP Doxy | No PEP | P value |
|------------------------------|-------------|-------------|-------------|
| SITE PCR + | | | |
| Anus | 11 | 19 | |
| Throat | 15 | 12 | |
| Urine | 1 | 7 | |
| Total sites | 27 | 38 | |
| Total infections | 27 | 30 | |
| Infections per 100 py | 32.6 | 37.3 | 0.63 |

Molina et al Lancet ID 2018

Molina – “To doxyPEP or Not to doxyPEP – That is the Question” – IUSTI Europe Webinar #21

<https://www.iusti-europe.eu/web/index.php/webinar-recordings/webinar-21/201-to-doxyep-or-not-to-doxyep>



Gonorrhoea Results: Monthly SF cases among MSM and TGW



CROI 2024



AMR in STIs

Syphilis (TP):

- **Clinical failure to Doxy (n=1)**
 - Early latent neurosyphilis, 2 courses doxy (2w & 4w)

CT: no evidence of CT AMR presently

- Treatment failures ↓ Tc susceptibility
- Tc-R between CT in pigs, fish meal with Tc
- Doxycycline most effective treatment for CT

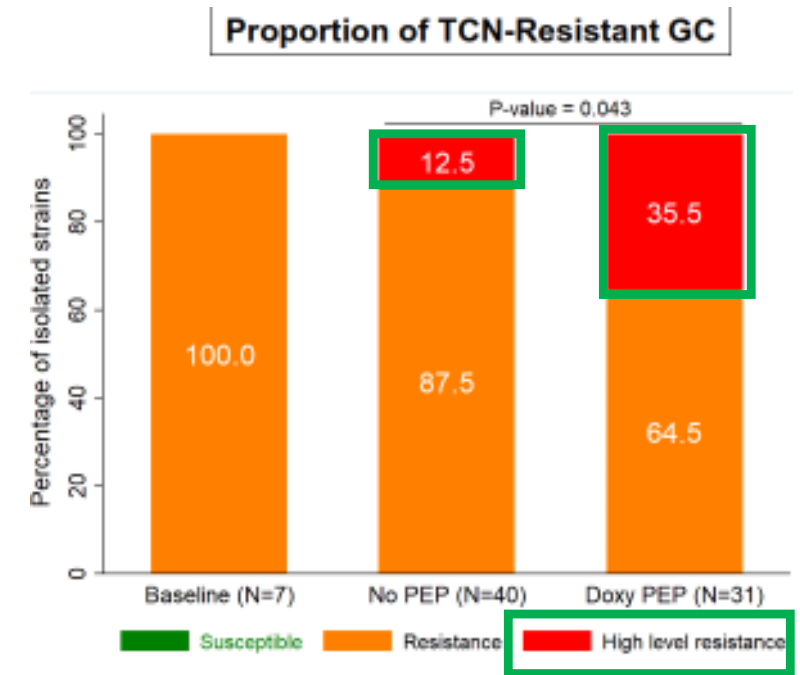
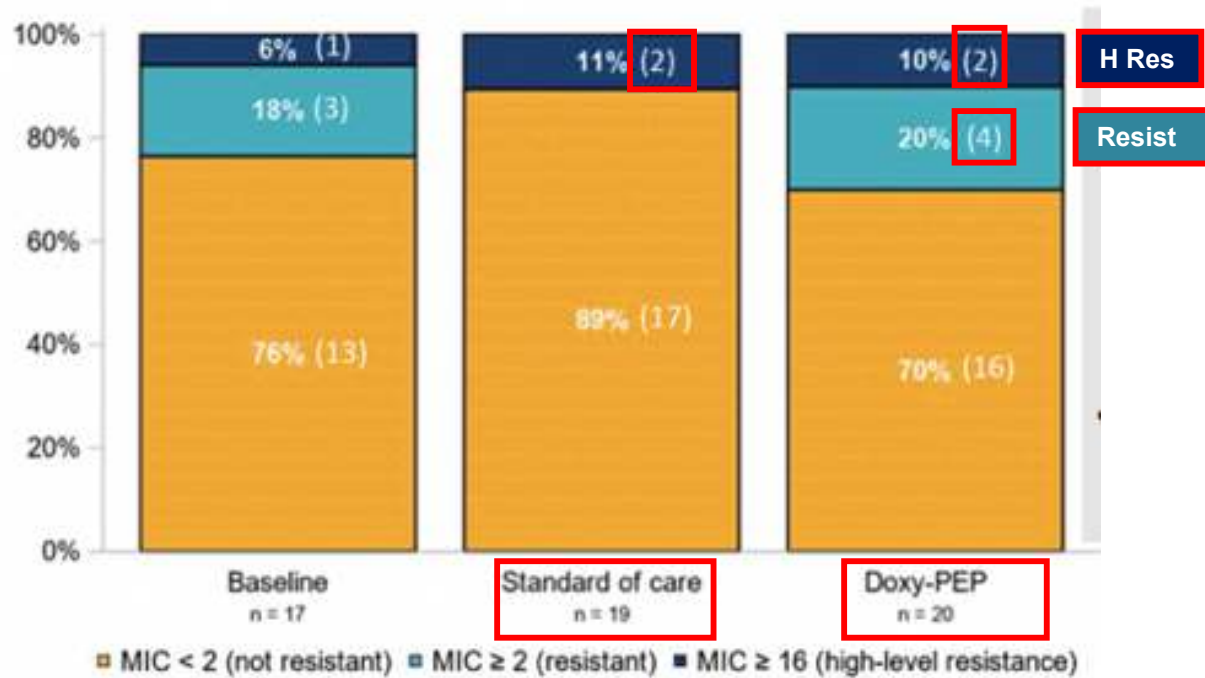
Select XDR **Shigella** (*sonnei*) [87.5% Tc-resistant]

(1) Zenilman et al *STD* 1993 (2) Wang SA, *J Infect Dis* 2005 (3) Bhengraj AR *Chemotherapy* 2010 (4) Jones RB *J Infect Dis* 1990 (5) Lefevre JC *Sex Transm Dis* 1998 (6) Somani J, *J Infect Dis* 2000 (7) Seth-Smith HMB *Genome Biology and Evolution* 2017 (8) Lefevre S. *Nature Comm* 2023



AMR in STIs (cont.)

NG: In DoxyPEP: Slightly higher NG Tc-R in doxy arm but low sample size



DOXYPEP

DoxyVAC (CROI2024)



AMR in STIs (cont.)

NG: Kenya study – pTetM / pblaTEM in 97%/55% isolates (n=103), assoc. with **doxy empirical treatment**

MG: Doxy used 1st then add 2nd drug (macrolides or fluroquinolone)

- Doxy cures ~30-40% of MG
- AMR in MG ↓ affects other Tc e.g. **minocycline**
- IPERGAY sub-study: mutations associated with Tet-R in other bacterial species, enhanced in doxy users

(1) Cehovin A et al, JID 2018 (2) Jensen J et al *JEADV* 2022 (3) Geisler W. *STI Post-Exposure Prophylaxis with Doxycycline Consultation Agenda: NACCHO* (4) Bercot B et al. *CID* 2021



AMR is a threat to human health (WHO)

- AMR:
 - Costly: US\$3.4 trillion/year by 2030
 - Deadly: 1.3-5.0mil (2019) → (2050) 10mil/yr ≈ global cancer deaths in 2020
 - Deaths from 6 bacteria: **human commensals**:
 - *E.coli*, *S.aureus*, *K.pneumoniae*, *S.pneumoniae*, *A.baumannii*, and *P.aeruginosa*
- 10days doxy: 100-fold ↓ bifidobacteria, ↑ Tc-R in gut commensal
- Tc-R in **mouth**(Strept), **gut**(*E.coli*), **resp** tract(5.8x ↑ Tc-R)
- Use in **acne**
 - Select for Tc-resist NG (25% NG 'bystander') and ↑ AMR in acne
 - Significant ↑ URTI (OR 2.8), female UTI (OR 1.9), pharyngitis (OR 4.3)
- Use in **malaria**: Tc-R in *S.aureus* and *E. coli*

(1) UNEP. Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance 2023 (2) Murray et al. *Lancet* 2022 (3) Saarela M, et al. *Int J Antimicrob* 2007 (4) Truong R et al. *JAC Antimicrob Resist* 2022 (5) Tedijanto C et al. *Proc Natl Acad Sci U S A* 2018 (6) Farrah G et al. *Dermatol Ther* 2016 (7) Bhate K, *BJGP open* 2021 (8) Lesens O et al. *Emerg Infect Dis* 2007 (9) Vento TJ et al. *BMC Infect Dis* 2013



Commensal AMR – baseline to month 12

- **S. aureus (not MRSA):**
 - DoxyPEP: Doxy-R ↑ from **4% to 12% (p<0.05)**
 - Control – no significant change
- Commensal *Neisseria* in oropharynx
 - **Mth 12: DoxyPEP vs control – 70% vs 45 % (p<0.05)**
 - DoxyPEP: Doxy-R ↑ from 63% to 70% (p=0.2)
- Resistance to other antibiotics
 - Control (n=19): Pen (n=2)
 - **DoxyPEP (n=20): Pen (n=1), azithro (n=3), cipro (n=2)**
 - No resistance to ceftriaxone/cefixime

REF CROI 2023: https://www.aidsmap.com/news/feb-2023/no-marked-increase-gonorrhoea-resistance-doxysep-study?utm_source=conference+news-english&utm_medium=email&utm_campaign=2023-02-21

AMR DoxyPEP CROI 2023 https://www.natap.org/2023/CROI/croi_11.htm



Speed up NG AMR spread & cross-resistance

- DoxyPEP accelerate spread of doxy AMR in NG
... if select all Tc-R: ↑ AMR to **other** antibiotics
- MSM: 63% (214/340) NG - intermediate Tc MIC
 - **‘Reservoir for rapid evolution of resistance’**
- NG: ↓ Tc suscept. had ↓ ceftriaxone suscept.

Antibiotic consumption

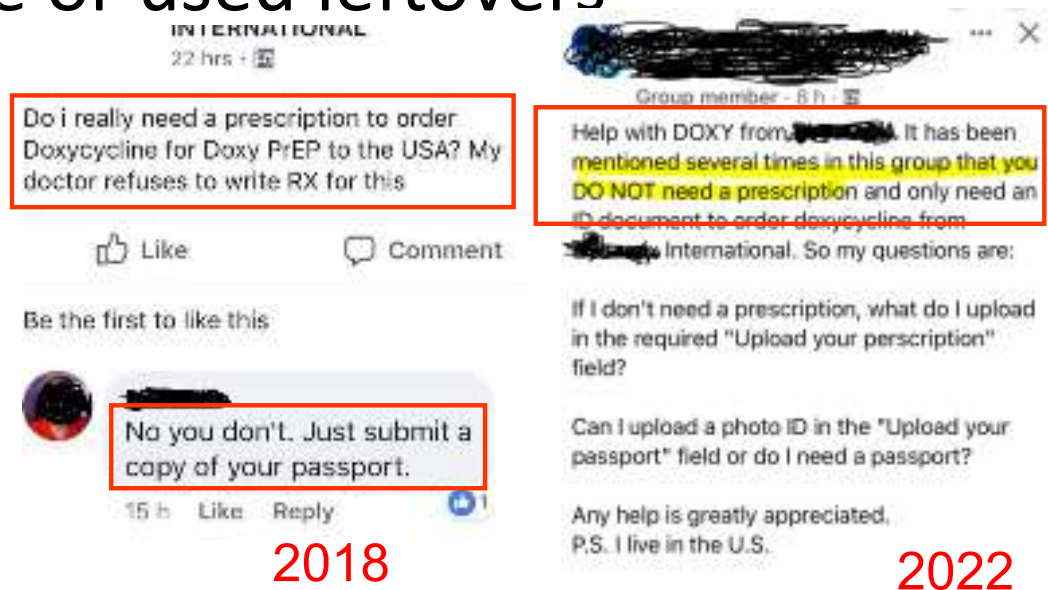
- DoxyPEP does not prolong life of ceftriaxone
- ↓ ceft & azithro use at cost of high doxycycline use

(1) Reichert E et al. **PREPRINT** <https://doi.org/10.1101/2023.04.24.23289033> (2) Mortimer T et al. CID 2023 DOI <https://doi.org/10.1093/cid/ciad279> (3) Vanbaelen T et al. STD 2023 <https://doi.org/10.1097/OLQ.0000000000001810> (4) Whiley et al, LancetID 2023 [https://doi.org/10.1016/S1473-3099\(23\)00359-6](https://doi.org/10.1016/S1473-3099(23)00359-6)



High consumption and poor antibiotic stewardship

- DoxyPEP: 25% took ≥ 10 doses/month
- ~8-10% of PrEP users (London, Melbourne and Amsterdam) use Doxy
- Used amoxicillin, azithromycin or ciprofloxacin as PEP.
- Many purchased online or used leftovers
- Buying online without prescriptions



(1) Chow EPF, *The Lancet HIV* 2019 (2) Carveth-Johnson T, et al. *Lancet HIV* 2018 (3) Evers YJ, et al. *Sex Transm Infect* 2020 (4) Vanbaelen T et al. *Sex Transm Infect* 2022

Summary

- ‘Noise’ of AMR using DoxyPEP
- Needs ongoing AMR surveillance
 - STIs and commensals
- Individual effects vs population effects
 - Not for everyone, target use e.g. those with TP
- Educate on AMR and DoxyPEP e.g. doesn’t cure NG
[Tc-R high: UK=75%, AUS=41%^{VIC=51%}]



NG Effectiveness in EU

- EUCAST MIC >0.5mcg/mL (tetracycline resistance)
- ~63% isolates resistant [<50% = 'effective']

| 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. ^aBased 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). ^bBased on the clinical tetracycline resistance breakpoint (MIC > 1.0 mg/L) stated by the US Clinical and Laboratory Standards Institute (www.clsi.org). ^cTetracycline 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. Unemo 2024 Lancet <https://doi.org/10.1016/j.lanepe.2024.100871>



Thank you

Associate Prof. Fabian Kong

Deputy Head, Sexual Health Unit

Centre for Epidemiology and Biostatistics

Melbourne School of Population and Global Health,

University of Melbourne

kongf@unimelb.edu.au

