Selection of *Neisseria gonorrhoeae* ceftriaxone resistance using doxycycline post-exposure prophylaxis

There is increasing evidence that doxycycline post-exposure prophylaxis (doxy-PEP) is effective for preventing sexually transmitted infections among high-risk patients, particularly in patients using HIV pre-exposure prophylaxis.[1–3] However, this benefit must be weighed against potential risks, including selection of antimicrobial resistance. Using whole genome sequencing data of 2375 gonococcal isolates from the 2018 Euro-GASP survey, Vanbaelen and colleagues[4] showed that *N gonorrhoeae* tetracycline resistance-associated mutations and genes are often co-selected with additional antimicrobial resistance markers. In addition, the authors highlighted that doxy-PEP can also select for other antimicrobial resistance in the absence of doxycycline or tetracycline resistance. Resistance, once established, is associated with strong clonal spread on many genomic backbones or genotypes. In this study, genomic genotypes included the well-recognised G1407 genogroup associated with decreased susceptibility to ceftriaxone. Ceftriaxone is the mainstay for *N gonorrhoeae* treatment globally and there are new reports concerning a surge of penA60-harboring ceftriaxone-resistant strains.[5–7] We sought to better understand the potential for selection of *N gonorrhoeae* ceftriaxone resistance through doxycycline treatment.

Firstly, we reviewed published data for penA60-harboring ceftriaxone-resistant strains reported to date (appendix pp 1, 2). These data show that these strains were susceptible to tetracycline when first reported in Japan in 2015. Since this initial case, 32 more penA60 (and the more recently emerged and closely related penA237) reports have been published. Combined, this entails 96 isolates or strains from 14 countries, with tetracycline susceptibility data available for 75 (78·1%) of 96 reported strains. Of strains with tetracycline resistance data reported, only eight (10·7%) of 75 showed susceptibility to tetracyclines, with eight (10·7%) showing intermediate susceptibility, and 59 (78·7%) resistant to tetracyclines (using EUCAST and CLSI breakpoints for tetracycline). Secondly, we retrieved data from PubMLST for all isolates (n=4346) reporting both a complete multilocus sequence type and categorical tetracycline susceptibility.[8] Tetracycline resistance was observed in 62·9% of reported isolates and was widespread, occurring in many clonal backgrounds (appendix p 3). We also did retrospective tetracycline minimum inhibitory concentration (MIC) testing on all *N gonorrhoeae* isolates with decreased susceptibility or resistance to ceftriaxone (MIC values ≥0·125 mgL) from NSW, Australia, reported in 2015–22; and 64 (97%) 66 of these *N gonorrhoeae* isolates tested were tetracycline resistant.

Overall, these data add weight to the concerns raised by Vanbaelen and colleagues[4] and show that *N gonorrhoeae* strains with decreased susceptibility or resistance to ceftriaxone typically exhibit dual resistance to tetracyclines. Hence, there is a risk that increased use of doxy-PEP will select for dual resistant strains and increased ceftriaxone resistance.

The extent of *N gonorrhoeae* ceftriaxone resistance globally is unknown. The isolates reported very probably represent only a fraction of *N gonorrhoeae* diversity, given that antimicrobial resistance surveillance is known to be limited in many settings. Although these data potentially point to doxy-PEP selecting for ceftriaxone resistance, how quickly selection of dual resistant strains would occur is unknown. It is likely that this will depend on many factors, including how widespread the doxy-PEP use is, the populations in which it is used (including associated circulating gonococcal antimicrobial resistance profiles), and whether additional measures are put in place, such as complementing doxy-PEP with enhanced *N gonorrhoeae* antimicrobial resistance surveillance. Furthermore, the net effects that antimicrobial selection pressure will have on the circulating *N gonorrhoeae* clones, especially if doxy-PEP strategies are only focused on high-risk populations, is likewise unclear (particularly given antibiotic consumption, including doxycycline for treatment of other STIs, might already be much higher in populations at high risk), as is the use of antimicrobials (either intentionally or incidentally) on infections that are not prevented by use of doxy-PEP, and the contribution of these infections to gonococcal antimicrobial resistance.

Overall, the risk of selecting for dual resistant strains and increasing *N gonorrhoeae* ceftriaxone resistance needs to be carefully balanced against the benefits of using doxy-PEP to prevent and treat sexually transmitted infections. At the very least, consideration needs to be given to enhancing surveillance of *N gonorrhoeae* antimicrobial resistance in populations using doxy-PEP, including via the use of molecular testing strategies and whole genome sequencing.

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See **Online** for appendix

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