Response to the ASHM 2023 statement on the use of doxy-PEP in Australia: considerations and recommendations

In September 2023, the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) released the *2023 Consensus statement on doxycycline prophylaxis (doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual, and other men who have sex with men in Australia*,[1] which appears in this issue of the *MJA*.[2] The Statement addresses important considerations for the use of doxy-PEP to reduce acquisition, potential transmission, and negative sequalae primarily for syphilis, while noting its clinical benefit, albeit to a lesser extent, for chlamydial and gonococcal infection for gay and bisexual men who have sex with men (GBMSM). We commend ASHM on this timely and important statement, with people already requesting or using doxy-PEP, with or without clinical oversight. In response, we wish to further emphasise two important considerations for doxy-PEP implementation, notably, the potential threat of increasing antimicrobial resistance (AMR) and the urgent need to implement measures to effectively monitor doxy-PEP use and its impact.

Not all sexually transmitted infection prophylaxis strategies are equal

Chemoprophylaxis for human immunodeficiency virus (HIV) infection, administered as pre-exposure prophylaxis (PrEP) and/or post-exposure prophylaxis (PEP), is an effective, well tolerated and highly acceptable strategy for preventing HIV acquisition. For example, HIV PrEP use in the previous six months was reported by 77% of Sydney Gay Community Periodic Survey respondents living without HIV engaging in condomless anal intercourse with casual partners.[3] Despite implementation of primary and secondary prevention strategies, rates of notifiable bacterial sexually transmitted infections (STIs) continue to rise. Doxy-PEP could be similarly effective as a syphilis prevention strategy in GBMSM. Syphilis is highly prevalent in GBMSM and has the potential to cause neurological and cardiovascular disease if untreated.[4] Concerningly, modelling predicts that more than two-thirds of early syphilis infections among GBMSM in Australia remain undiagnosed and consequently untreated.[5] It is, however, important to highlight key differences between HIV PrEP and doxy-PEP, especially for the end user. The complexities of comparing these two interventions were discussed at the doxy-PEP consensus statement launch. HIV PrEP is highly effective and, although the development of AMR in HIV needs to be monitored, the benefits of drastically reduced HIV acquisition greatly outweigh the low risk of resistance. Furthermore, the collateral impacts of HIV PrEP (using tenofovir–emtricitabine-based treatment) versus a broad-spectrum antibiotic such as doxycycline differ considerably. Even though the impact of HIV PrEP on bystander viruses is not fully understood, no significant negative impacts on HIV prevention or other concerns in the sexual health field have been noted in the literature in the period that HIV PrEP has been used. Conversely, doxycycline has broad off-targeted activity against many bacteria, including commensals, with substantial potential to generate AMR not only in bacteria that cause STIs but in other bacterial species (pathogenic or commensal). This risk needs to be carefully weighed against the benefits of reduced syphilis incidence for GBMSM.

Antimicrobial stewardship, resistance and microbiota impacts

Globally, consensus is lacking on the use of doxy-PEP due to concerns around increased antimicrobial consumption and the development of AMR not just among bacteria that cause STIs but other pathogens (Supporting Information 1 and Supporting Information 2).[1,6-16] Although statements supporting the use of doxy-PEP acknowledge the risk of AMR, the true impact on AMR is yet to be adequately assessed, and studies thus far indicate significant potential for increased AMR in a number of important human pathogens.[17] Despite limited data, doxy-PEP trials demonstrate increases in tetracycline resistance among commensals including *Staphylococcus aureus* and *Neisseria* spp.[18,19] Evidence of AMR development has also been reported in people taking continuous prophylactic low dose doxycycline for malaria and acne[17] (a different dose regimen to doxy-PEP) and co-resistance observed to doxycycline, ceftriaxone and ciprofloxacin in *Klebsiella pneumoniae* in a doxy-PEP animal model.[20] Such outcomes are not unexpected, as it is well recognised that increased use of antibiotics often leads to increased AMR. Given the current state of evidence, it is important to ask if more caution be given to supporting and implementing doxy-PEP.

The ASHM Statement recommends considering doxy-PEP primarily for the prevention of syphilis in GBMSM, due to the morbidity attributed to syphilis being greater than chlamydia or gonorrhoea. Tetracycline resistance is rarely documented in *Chlamydia trachomatis* or *Treponema palladium*;[21] however, *Neisseria gonorrhoeae* can develop and maintain resistance to tetracyclines as well as the other antimicrobials, with mutations conferring co-resistance.[22] The Statement acknowledges doxy-PEP is unlikely to be an effective gonorrhoea control strategy, given high gonococcal tetracycline resistance (45%) in Australia,[23] with higher rates likely among GBMSM.[24] However, STI co-infection frequently occurs. For instance, multivariate analysis estimated that GBMSM with concurrent gonococcal or chlamydial infection had a 60% higher risk of syphilis compared with

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GBMSM without gonococcal or chlamydial infection.[25] Given the likelihood that gonococcal infections are frequently exposed to doxy-PEP, this potentially undermines gonococcal antimicrobial stewardship efforts by accelerating the spread of gonococcal AMR[26] and potentially selecting for multidrug-resistant gonococcal strains.[27] By averting gonorrhoea infection, the doxy-PEP study reduced ceftriaxone use by half in the doxy-PEP arm against a background of 20% *N. gonorrhoeae* tetracycline resistance at the time of the trial.[28] However, when rates of *N. gonorrhoeae* tetracycline resistance are higher, as was the case with the ANRS IPERGAY trial,[21] gonorrhoea incidence was not significantly different between the doxy-PEP and control arms. In the Australian context, with high rates of *N. gonorrhoeae* tetracycline resistance, doxy-PEP is unlikely to prolong the life of empiric treatments[26] and will also be at the cost of higher doxycycline consumption and higher rates of *N. gonorrhoeae* doxycycline and/or multidrug resistance.[29] In addition, the impact of doxy-PEP for the prevention of *Mycoplasma genitalium* infection has been largely overlooked. Despite the limited efficacy of doxycycline monotherapy for *M. genitalium*, with about one-third of infections being cured, doxycycline is an important part of the current treatment regimen of resistance-guided therapy and any reduction in efficacy of doxycycline for *M. genitalium* would have a substantial impact on the cure of an STI with already limited treatment options.[30] Although increases in doxycycline resistance have not been reported among small studies of *M. genitalium*, the molecular mechanisms of doxycycline resistance in this organism remain poorly understood,[31] precluding routine surveillance of doxycycline resistance in *M. genitalium*.

The effects of antimicrobials on the microbiome remain complex and have been associated with an increased risk of adverse outcomes.[32] A recent systematic review of AMR selection on human microbiota[33] with use of oral tetracyclines reported increases in tetracycline-resistant *Streptococcus* strains in subgingival flora, *Escherichia coli* in the gastrointestinal tract, and a 5.8-fold increase in tetracycline-resistant respiratory tract pathogens. Another randomised controlled trial found that doxycycline taken for ten days resulted in reduced gut bacterial diversity, including a 100-fold reduction in bifidobacteria, as well as increased prevalence of tetracycline resistance in gut commensals.[34] Doxy-PEP is also recommended for people living with HIV and the effects on the microbiome may be more complex in this group, who show an altered microbiome compared with those not living with HIV.[35] The addition of microbiota surveillance (eg, oral and rectal swabs to study orogastrointestinal microbiota) to other surveillance approaches is essential to quantify the effects on the human microbiota. Importantly, educating users of doxy-PEP about potential adverse effects on the microbiota as well as the development and spread of AMR should be an integral part of clinical consultations to enable genuine shared decision-making processes and should be included in comprehensive counselling and antimicrobial stewardship programs more broadly. The Box details suggestions for provider–client discussion points and information to address in doxy-PEP counselling as identified in existing documents.

Opportunities to enhance STI, AMR and antimicrobial use surveillance

The Statement listed nine recommendations for research, guidelines and policy.[1,2] We support the rapid ownership, development and adequate funding of these recommendations. In addition, we suggest systems be designed in line with the vision of One Health surveillance by undertaking standardised data collection methods or ensuring interoperable systems with not only other human health surveillance systems but also animal and ecosystem health surveillance systems.[36] This comprehensive approach would improve our understanding of the drivers of resistance; for example, the relative contribution of human and animal antimicrobial consumption on AMR.

The recommendation "pathology and public health bodies should be appropriately funded to monitor AMR" is critical, and timely action would ensure an agreed national minimum dataset to monitor the potential impacts of doxy-PEP on AMR and antimicrobial use and the roles and responsibilities being allocated to named agencies. Surveillance in Australia requires significant enhancements to monitor the impact of doxy-PEP use. The Australian model of sexual health care delivery, straddling state and Commonwealth providers and multiple unlinked databases, poses significant challenges for accurate surveillance.

Another recommendation highlights the need for development and deployment of molecular testing to monitor AMR. Identifying barriers and implementing solutions to support broad implementation of molecular AMR testing could supplement AMR surveillance and increase access to resistance-guided therapy.[37] However, existing commercial molecular antimicrobial susceptibility/resistance assays are predominantly designed to rule in and/or rule out use of a single antimicrobial, making them suitable for resistance-guided therapy but of lesser utility for AMR surveillance. Furthermore, given limited demand, commercial tests encompassing both resistance-guided therapy and AMR surveillance are yet to be developed. Government support would likely enable industry to accelerate the development of AMR tools, providing a timely solution for pathology laboratories to enhance AMR surveillance and to support clinical implementation of resistance-guided therapy, including in the context of doxy-PEP use. Given the prohibitive cost of molecular AMR testing comparative to molecular pathogen identification, pathology cost subsidies by relevant federal or jurisdiction governments would support the uptake of molecular AMR testing. Such an outcome would be particularly beneficial for regional and remote areas under-represented in culture-based AMR surveillance.

The use of doxy-PEP now seems unavoidable. However, implementation of doxy-PEP without adequate access to STI testing, including AMR testing and adequate antimicrobial use surveillance systems, warrants

Counselling topics for clinicians to discuss with clients considering doxycycline post-exposure prophylaxis (doxy-PEP) for sexually transmitted infections (STIs)

Counselling discussion topic	Reference
Doxy-PEP not recommended	7
No evidence for use of alternate antibiotics	1,7,16
No evidence for STIs other than chlamydia or syphilis	7
Doxycycline not safe in pregnancy, contraception required/avoid pregnancy	7,8,10,13
Efficacy	8,11,13
Potential benefits	11,16
Side effects (photosensitivity, pill esophagitis, other rare side effects)	8,10,11,13,14,16
Drug interactions	8,10,11,13,14
Dosing regimens	11
Strategies to minimise use of doxy-PEP	1
Consider episodic treatment for higher risk periods	1,11
Unknown effect on gut microbiome, commensal organisms and other STIs	8,11-13,15
Unknown long term effect on individual and population STI AMR	1,8,11-15
Doxycycline formulations and availability	14
Immediate release doxycycline less expensive	8,13
Take with fluid, food increases tolerability	11
Ongoing monitoring	11
Preventive sexual health education, screening, vaccination, HIV PEP and/or HIV PrEP, expediated partner therapy, HIV treatment for PLWH	10-14
Alternative STI prevention, diagnosis, treatment options	11
Counselling discussion not addressed	9

AMR = antimicrobial resistance; HIV = human immunodeficiency virus; PEP = post-exposure prophylaxis; PLWH = people living with HIV; PrEP = pre-exposure prophylaxis. ◆

increased vigilance. Ultimately, economic and political prioritisation is the cornerstone to realising meaningful antimicrobial stewardship outcomes. Particular attention must be given to the national design and implementation of enhanced surveillance of AMR and antimicrobial use in STIs as well as commensal organisms and non STI pathogens that are associated with considerably higher mortality and morbidity than STIs. Recommendations for doxy-PEP should be comprehensive, citing all available evidence including inconclusive findings. We support community-developed resources outlining potential benefits and risks to individual and public health in the short and long term for GBMSM considering doxy-PEP use. Until such time, we encourage clinical consultations to engage in two-way dialogue around sexual risk and antibiotic use, given the threats discussed herein.

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[Correction added on 26 March 2024, after first online publication: Provenance section has been added]

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Supporting Information

Additional Supporting Information is included with the online version of this article.