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Supporting Information 3

Supplementary material

**This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.**

Appendix to: Cornelisse VJ, Riley B, Medland NA. Australian consensus statement on doxycycline post-exposure prophylaxis (Doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual and other men who have sex with men. *Med J Aust* 2024; doi: 10.5694/mja2.52258.

ASHM Roundtable on Doxy-PEP — Report

Executive Summary

On 17 March 2023, ASHM held a roundtable discussion on biomedical STI-prevention strategies using doxycycline, or Doxy-PEP. The roundtable brought together community representatives, clinicians, and experts in infectious diseases, public health, epidemiology, and antimicrobial stewardship, to review relevant data, exchange expertise, and develop guidance on the utility and potential risks of Doxy-PEP. Key themes from the discussion are outlined below.

AMR and microbiome	• Clinicians have a responsibility to the community and to their patients to consider AMR when prescribing antibiotics for any purpose. • AMR should be discussed with patients sensitively and as a population issue, rather than assigning responsibility to individual Doxy-PEP users. • It is unknown what impact Doxy-PEP use may have on the gut microbiome of individual users, who should be informed of potential harm. • Gonococcal AMR surveillance must be strengthened in order to monitor potential increases in antibiotic-resistant strains of gonorrhoea.

Clinical	• Guidelines for Doxy-PEP prescribing should consider differences in STIs in developing suitability criteria, as syphilis confers a much greater burden of morbidity among GBMSM than either chlamydia or gonorrhoea.
	• Suitability criteria might be:
	  ○ GBMSM with a recent syphilis diagnosis (e.g., within the previous six or twelve months); or
	  ○ GBMSM with two or more recent other (i.e., not syphilis) bacterial STI diagnoses (e.g., within the previous six or twelve months); or
	  ○ GBMSM who identify an upcoming period of heightened STI risk, for example, attendance at a sex event, or holiday plans that likely involve sexual activity with multiple casual sexual partners; or
	  ○ GBMSM with concurrent male and cisgender female sexual partners or other sexual partners with a uterus, recognising the additional health risks posed by chlamydia, gonorrhoea and syphilis for people with a uterus.
	  ○ GBMSM who present for HIV PEP can also consider Doxy-PEP, although the indications for HIV PEP do not necessarily indicate a need for Doxy-PEP.

	• Clinicians should be supported with up-to-date information to discuss AMR with patients where appropriate.
Community	• Having multiple choices for STI-prevention strategies is a priority for GBMSM communities, and Doxy-PEP should be considered as part of a range of options. • Communities should have access to comprehensive information on how to use Doxy-PEP as effectively and safely as possible. • Proactive strategies should be deployed to prevent Doxy-PEP-related stigma inside and outside clinical settings, through education of community and clinicians.
Education	• Clinical education about Doxy-PEP can be integrated into existing sexual health education, including clinical guidelines, decision-making tools and training courses. • Doxy-PEP education should be co-designed by clinicians and community, to ensure information aligns across available resources.

1 Background

On 17 March 2023, ASHM held a national roundtable discussion on biomedical STI-prevention strategies using doxycycline, or Doxy-PEP and Doxy-PrEP. This report summarises the issues discussed at that roundtable, and accompanies a consensus statement developed as a result of consultation with stakeholders at that event.

Doxy-PEP and Doxy-PrEP refer to the use of doxycycline as either post-exposure (PEP) or pre-exposure (PrEP) prophylaxis to prevent bacterial STIs, namely chlamydia, gonorrhoea and syphilis. "Doxy-PEP" will be used throughout this report to refer to both strategies except where the distinction is of particular importance. Increasing evidence shows that Doxy-PEP is highly effective as a prevention strategy for some bacterial STIs. However, there remain several unanswered questions around potential adverse outcomes, including the possibility of inducing antimicrobial resistance (AMR) in STIs and other "bystander" organisms or disrupting the user's microbiome.

The available evidence regarding Doxy-PEP was summarised in an ASHM interim position statement developed in early 2023 and published in *Sexual Health*[1]. One of the recommendations from this interim statement was to convene a forum of community representatives, clinicians, and experts in infectious diseases, public health, epidemiology, and antimicrobial stewardship, to review relevant data, exchange expertise, and develop guidance on the utility and potential risks of Doxy-PEP. This document describes discussion points from this subsequently convened forum.

The day was structured in two parts, beginning with presentations from speakers to cover key issues relevant to the outcomes of the day. These included: summary of clinical trial evidence on Doxy-PEP; general background on AMR and STIs; modelling the potential impact of Doxy-PEP on population prevalence of STIs; and community attitudes to and needs from Doxy-PEP. Following these presentations, attendees split into small groups to identify and discuss issues grouped by theme, and then reported back to the main group for discussion by all attendees.

Due to the evidence base for Doxy-PEP primarily covering gay and bisexual men who have sex with men (GBMSM), discussion on the day focused on the impact of Doxy-PEP for these communities.

However, ASHM recognises that some other communities also experience a high burden of STIs, including rural and remote Aboriginal and Torres Strait Islander communities, and the Trans and Gender Diverse community. Doxy-PEP may be a useful strategy for those communities, but the potential implementation of Doxy-PEP in these communities will require further consideration and development of an evidence base that involves people from those communities.

2 AMR and microbiome

Clinicians have a responsibility to the community and to their patients to consider AMR when prescribing antibiotics for any purpose, and to ensure that their clinical practice adheres to principles of antimicrobial stewardship. Many members of the public have misconceptions about drug resistance—doctors should ensure that patients who are considering Doxy-PEP are

[1] Cornelisse VJ, Ong JJ, Ryder N, Ooi C, Wong A, Kenchington P, et al. Interim position statement on doxycycline post-exposure prophylaxis (Doxy-PEP) for the prevention of bacterial sexually transmissible infections in Australia and Aotearoa New Zealand - the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Sexual health. 2023.

able to make balanced decisions based on correct information about AMR. Similarly, agencies which work with GBMSM and their health providers should aim to sustain and improve community health literacy related to AMR.

Assumptions about the benefit of testing and treating for asymptomatic chlamydia and gonorrhoea (and *Mycoplasma genitalium*) in GBMSM are currently being challenged, particularly because these STIs often do not cause adverse health outcomes for infected GBMSM, and screening, testing and treatment for these asymptomatic STIs has resulted in very high levels of antibiotic consumption in the GBMSM community. There is also lack of strong evidence to indicate that screening for chlamydia and gonorrhoea is effective in reducing incidence and prevalence of these STIs. This highlights that concerns around AMR relating to Doxy-PEP use must similarly consider whether the current test-and-treat strategy for asymptomatic chlamydia and gonorrhoea remains appropriate.

Based on data from clinical trials on Doxy-PEP, it is projected that Doxy-PEP use will result in increase annual consumption of antibiotics (doxycycline) for most users. However, at a population level, if doxy-PEP is appropriately targeted at people who carry the highest burden of STIs, then doxy-PEP could interrupt STI transmission networks and could result in population-level declines in STI diagnoses, which could, in the long term, result in a population-level reduction in antibiotic consumption to treat STIs.

It is appropriate for doctors to discuss AMR and antibiotic stewardship with individual patients in consultations relating to the use of Doxy-PEP. However, balancing specific individual benefit against uncertain community harm is difficult and largely theoretical. This should be done sensitively to avoid stigmatising individuals who are taking or asking about Doxy-PEP, including acknowledgement that significant uncertainties exist. AMR could be discussed as a population issue, while being careful to avoid assigning individual responsibility to Doxy-PEP users.

The long-term use of Doxy-PEP has not been studied and there is a plausible potential for individual-level harm related to disruption of the intestinal microbiome. The science of the gut microbiome is complex and still developing, and this potential harm should be a research priority. Users of Doxy-PEP should be informed about this potential harm.

In Australia, doxycycline is not used to treat gonorrhoea. However, it has been observed that strains resistant to doxycycline are more likely to also be resistant to antibiotics that are used to treat gonorrhoea. It is not yet clear what microbiological mechanism, if any, underlies this correlation. In theory, selection for such multi-resistant strains in a population with high exposure to doxycycline could increase the prevalence of resistance to those antibiotics that are used to treat gonorrhoea. This potential harm should be a research priority.

Given the considerations outlined above, it is clear that gonococcal AMR surveillance needs to be strengthened: although Australia has world-leading gonococcal AMR surveillance, only a

minority of gonorrhoea diagnoses are accompanied by culture and antibiotic susceptibility testing. To ensure appropriate surveillance for gonococcal AMR, all gonorrhoea diagnoses in Doxy-PEP users should be monitored for AMR. If possible, use of doxy-PEP should be recorded and reported alongside antibiotic resistance data. Guidelines recommend culture testing of all anatomical sites that are (potentially) infected with gonococci, e.g. the pharynx, anorectum and urethra. Additionally, given the relative insensitivity of culture testing, molecular testing for gonococcal AMR should be developed and implemented, ideally as reflex tests on any samples positive for gonococci by PCR.

3 Clinical

There are currently no Australian or New Zealand clinical guidelines to inform clinical practice for Doxy-PEP prescribing. A range of considerations should inform their development, including suitability criteria, AMR considerations, testing, and STI monitoring and surveillance.

A fundamental consideration is whether all bacterial STIs warrant a biomedical intervention, or whether instead Doxy-PEP is best implemented as a syphilis prevention strategy, which is the bacterial STI with greatest morbidity among GBMSM. Such considerations should inform the development of optimal suitability criteria for Doxy-PEP.

Suitability criteria will need to account for individual patient health and population health, which includes AMR considerations. Mathematical modelling might help to inform the targeting of suitability criteria to maximise the potential impact on population level STI rates, while avoiding use that is unlikely to be beneficial.

Informed by mathematical modelling, suitability criteria might be based on factors including:

- GBMSM with a recent syphilis diagnosis (e.g., within the previous six or twelve months); or
- GBMSM with two or more recent other (i.e., not syphilis) bacterial STI diagnoses (e.g., within the previous six or twelve months); or
- GBMSM who identify an upcoming period of heightened STI risk, for example, attendance at a sex event, or holiday plans that likely involve sexual activity with multiple casual sexual partners; or
- GBMSM with concurrent male and cisgender female sexual partners or other sexual partners with a uterus, recognising the additional health risks posed by chlamydia, gonorrhoea and syphilis for people with a uterus.
- GBMSM who present for HIV PEP can also consider Doxy-PEP, although the indications for HIV PEP do not necessarily indicate a need for Doxy-PEP.

HIV status and PrEP use alone do not seem to predict STI risk, however, it is important that anyone who commences Doxy-PEP is also given access to either HIV treatment or HIV PrEP, depending on their HIV status.

When Doxy-PEP is not clearly indicated to prevent syphilis, clinicians may consider prescribing based on other factors. These may include high levels of anxiety about STIs or partner notification, for example. Hypothetical clinical scenarios may be one way of communicating this information, and could be used in guidelines to illustrate a range of examples. Given the current evidence, suitability criteria should not be a strict framework for refusing to prescribe Doxy-PEP. However, they can be a helpful framework for prompting discussions to explore possible reasons for patients requesting Doxy-PEP, and may lead to a mutual decision with a patient not to prescribe in some circumstances.

Where knowledge about Doxy-PEP within communities is high, clinical recommendations and resources should support clinicians to engage with requests from patients. Determining suitability in these cases can be informed by taking a sexual history and a history of previous STIs, and further discussion about why a patient might be seeking Doxy-PEP, including psychosocial factors. Consideration should also be given to whether Doxy-PEP or Doxy-PrEP may be more suitable for a specific patient. In general, given the currently available evidence, Doxy-PEP is preferable over Doxy-PrEP, as the former is an effective strategy that uses lower quantities of doxycycline than Doxy-PrEP.

Some clinical trial evidence has indicated the effectiveness Meningococcal B vaccination (MenB) to protect against gonorrhoea. However, this is an area of ongoing investigation. Further, MenB vaccines are not currently available on the PBS and may not be affordable for some patients.

Several critical questions for clinical practice relate to AMR, and these should be addressed in clinical guidelines:

- To what extent should AMR considerations inform prescribing Doxy-PEP for specific patients?
- When and how should a clinician discuss AMR with a patient seeking Doxy-PEP?
- Should AMR considerations inform conversations with patients who do not meet suitability criteria for prescribing, and how so?
- Do clinicians need to monitor for the emergence of AMR, in both STIs and bystander organisms; and if so, how can this be done most effectively?

There is precedent for discussing AMR with patients in general antibiotic prescribing, for example respiratory tract or urinary tract infections. That is, clinicians have experience in explaining to patients that clinicians have responsibility for antibiotic stewardship that extends beyond the individual patient. Resources from other areas of antibiotic stewardship may be

available to assist clinicians in conducting these conversations in a manner that is sensitive to the patient's needs.

Further, GBMSM have expressed interest in understanding more about AMR, as it may impact their own health or the health of their communities. It is important for clinician and patient that these conversations are informed by accurate, up-to-date information, particularly given reports of misinformation about AMR. These conversations should make clear the distinction between the impact of Doxy-PEP prescribing on the health of the individual patient and on broader patterns of AMR within the community, and the fact that these concerns will always be difficult to quantify.

Guidelines, clinical/community education and clinicians should be clear that Doxy-PEP is only partially effective at preventing gonorrhoea and that antibiotics other than Doxy-PEP are not likely to be effective or otherwise suitable as STI prophylaxis.

4 Community

GBMSM communities in Australia have been discussing and using Doxy-PEP for several years, and desire further education and guidance on its use. Sexual health literacy among GBMSM is generally high. Approaches to STI prevention, including Doxy-PEP, should be led by communities in partnership with clinicians, scientists, researchers and governments. At the same time, the "community" is not a homogenous group, and there are differing views within GBMSM communities on Doxy-PEP and on its relationship to AMR and microbiome effects.

Choice of STI prevention strategies is a priority for GBMSM communities, just as it is for HIV prevention. Doxy-PEP offers an additional option for STI prevention that will appeal to some GBMSM. Different people will have different requirements for prevention based on different life circumstances, such as relationship status or current sexual practices. Education and guidelines on Doxy-PEP should recognise that a person's need for Doxy-PEP can vary over time. For example, some people may wish to utilise Doxy-PEP for short periods of time when they perceive a heightened STI risk, such as during holidays or other periods of increased sexual activity; whereas other people may wish to utilise Doxy-PEP on an ongoing basis during their day-to-day life. Further, the burden of STIs among GBMSM differs across specific STIs and individuals. For example, syphilis is an STI of more concern within GBMSM communities compared with chlamydia, and considerations about Doxy-PEP use should account for these differences. It is also important to note the impact of structural barriers on the ability of communities to choose specific STI-prevention strategies, and that making additional strategies available may be a way of addressing those barriers.

Guidance relating to Doxy-PEP use should reflect these different patterns of use, such as differences in how to use doxycycline as PrEP or as PEP. This includes clear information on dosing regimens for each strategy, and a comparison of potential side-effects for the individual user (such as photosensitivity and oesophagitis), and potential risks to the community associated with AMR. Education developed by and provided to GBMSM communities in relation to HIV PrEP can provide a useful template, as this also describes different regimens (daily, on-demand) depending on individual preferences and life circumstances.

A harm reduction approach to STI prevention requires that those considering Doxy-PEP have access to comprehensive information about how to use it as effectively and safely as possible for their circumstances.

All communities deserve access to healthcare that is non-judgemental and without stigma. The rollout of HIV PrEP in Australia and elsewhere demonstrated that new sexual health strategies targeting GBMSM communities have the potential to lead to stigmatising interactions inside and outside of clinical settings. Implementation of Doxy-PEP in GBMSM communities must be accompanied by proactive strategies to prevent Doxy-PEP-related stigma, through education of community and clinicians.

GBMSM communities are aware of and hold diverse views towards AMR concerns associated with Doxy-PEP, and AMR concerns cause some GBMSM to be hesitant about its use. Many GBMSM also factor AMR-associated risks into how to use Doxy-PEP. These considerations may align with proposed eligibility criteria for prescribing that account for individual STI risk or burden. There are gaps in knowledge about AMR within GBMSM communities, such as concerns that AMR can develop in an individual (rather than in the organisms they carry) as a result of antibiotic use. There was a desire in general to understand more about AMR, such as via the different implications for Doxy-PrEP compared with Doxy-PEP, or short-term compared to long-term use.

The diversity of views about AMR within GBMSM communities requires community-level responses, not just individual ones. As well as considering the implications of AMR for Doxy-PEP prescribing and use, GBMSM communities can work towards building consensus on how the community as a whole should respond to the problem of AMR, and engage in collaborative conversations with clinicians and researchers. These conversations will need to be broader than focussing on Doxy-PEP alone, and, for example, involve considerations about asymptomatic STI screening, syndromic treatment of STI symptoms, and treatment of sexual contacts.

5 Education

Approaches to Doxy-PEP education are well-positioned to build on Australia's already strong partnerships between community, clinicians, researchers and governments. This partnership approach has been a cornerstone of the Australian response to HIV and STI prevention, exemplified by the rapid rollout of HIV PrEP, and is emphasised within Australia's Fourth National STI Strategy as a guiding principle underpinning the success of the Australian response. Education relating to Doxy-PEP should be developed in accordance with this partnership approach.

Doxy-PEP education can be integrated into existing education and resources that are already accessed by prescribers. Messaging about Doxy-PEP can be embedded into:

- Australian STI Management Guidelines
- Decision-making tools
- STI-related training courses
- HIV PrEP education
- HealthPathways
- eTG guidelines

Additional education for the clinical workforce may be required for prescribers in rural and remote areas, where patients have less choice about where to access care.

While HIV PrEP campaigns have been designed for harm reduction education and demand generation to achieve very broad uptake across GBMSM communities, the individual risk-benefit calculation for Doxy-PEP is very different from that for HIV PrEP, and hence Doxy-PEP is relevant to a smaller subset of GBMSM. As such, education should target these populations and focus on harm reduction and should clearly explain how Doxy-PEP is conceptually different from HIV PrEP. Community experience with messaging and promulgation for HIV PrEP education can inform the development of Doxy-PEP education. Further, given the already significant demand on sexual health services in Australia, capacity issues need to be considered if education is likely to generate increased demand for Doxy-PEP.

It is likely that GBMSM communities will be a primary source of education about Doxy-PEP for prescribers, driven by patients who are seeking it. Conversely, GBMSM communities also seek information about sexual health from clinical sources. As such, Doxy-PEP education developed by and for GBMSM communities should align with clinical education, and vice versa.