TITLE PAGE

**UK National Guideline for the Use of Doxycycline Post‑Exposure Prophylaxis (DoxyPEP) for the Prevention of Syphilis**

**Authors/Affiliations:**

* John Saunders/Blood Safety, Hepatitis, STIs and HIV Division, UK Health Security Agency
* Joseph Deering/ HCRG Care Group
* Claire Dewsnap/Sheffield Teaching Hospital Foundation Trust
* Rachel Drayton/Department of sexual health, Cardiff and Vale University Health Board, Cardiff, UK
* John Gilmore/School of Nursing, Midwifery and Health Systems, University College Dublin, Ireland
* Alison Grant/Pharmacist, Guy’s & St. Thomas’ NHS Foundation Trust, London
* Dwayne-Wilson Hunt/Chelsea and Westminster NHS Foundation Trust, London
* Manik Kohli/Institute for Global Health, University College London & Mortimer Market Centre, Central and North West London NHS Foundation Trust
* Fiona Lyons/National Clinical Lead, HSE Sexual Health Programme, Ireland
* Hamish Mohammed/Blood Safety, Hepatitis, STIs and HIV Division, UK Health Security Agency
* Phil Samba/The Love Tank CIC
* Benjamin Weil/The Love Tank CIC
* John White/Departments of GUM/HIV Medicine, Northern & Western Health & Social Care Trusts, Northern Ireland, UK
* Nicholas Medland/Kirby Institute, University of New South Wales, Sydney, Australia
* Helen Fifer/Blood Safety, Hepatitis, STIs and HIV Division, UK Health Security Agency

**Clinical Effectiveness Group, British Association for Sexual Health and HIV**

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| **Short Title:** DoxyPEP Guideline for the prevention of Syphilis |
| **CEG Editors:** Helen Fifer and Nicholas Medland |
| **Lead author:** John Saunders |
| **Version No.:** Consultation Draft |
| **Version Date:** 7th January 2025 |

1. TABLE OF CONTENTS

[TITLE PAGE 1](#_Toc181199818)

[1. TABLE OF CONTENTS 2](#_Toc181199819)

[2. ABSTRACT 4](#_Toc181199820)

[3. ABBREVIATIONS 5](#_Toc181199821)

[4. SUMMARY OF RECOMMENDATIONS 7](#_Toc181199822)

[5. INTRODUCTION AND METHODOLOGY 8](#_Toc181199823)

[5.1. Objectives 8](#_Toc181199824)

[5.2. Search strategy 8](#_Toc181199825)

[5.3. Methods 8](#_Toc181199826)

[5.4. Equality impact assessment 9](#_Toc181199827)

[5.5. Stakeholder involvement, piloting, and feedback 9](#_Toc181199828)

[6. EFFICACY 10](#_Toc181199829)

[7. SAFETY 12](#_Toc181199830)

[7.1. Safety and tolerability evidence from randomised clinical trials 12](#_Toc181199831)

[7.2. Side effects 12](#_Toc181199832)

[7.3. Long‑term safety 12](#_Toc181199833)

[7.4. Antimicrobial resistance 13](#_Toc181199834)

[8. BASELINE ASSESSMENT 15](#_Toc181199835)

[8.1. Considerations for doxyPEP use across different populations 15](#_Toc181199836)

[8.2. Health equity considerations 15](#_Toc181199837)

[8.2.1. Dosage and administration 16](#_Toc181199838)

[8.2.2. Baseline screening and diagnostic 16](#_Toc181199839)

[8.2.3. User education and support 17](#_Toc181199840)

[9. MONITORING AND FOLLOW-UP 18](#_Toc181199841)

[9.1.1. Follow-up and monitoring 18](#_Toc181199842)

[9.1.2. Coding and data collection 19](#_Toc181199843)

[9.2. Recommendations for non-specialist providers 19](#_Toc181199844)

[10. AUDITABLE OUTCOME MEASURES 20](#_Toc181199845)

[11. RECOMMENDATIONS FOR FUTURE RESEARCH 21](#_Toc181199846)

[11.1. Implementation and impact 21](#_Toc181199847)

[11.2. Antimicrobial resistance and monitoring 22](#_Toc181199848)

[12. DISCLOSURES 23](#_Toc181199849)

[12.1. Acknowledgements 23](#_Toc181199850)

[12.2. Declaration of Conflicting Interests 23](#_Toc181199851)

[12.3. Funding 23](#_Toc181199852)

[12.4. Editorial Independence 23](#_Toc181199853)

[12.5. Membership of the Clinical Effectiveness Group 23](#_Toc181199854)

[12.6. ORCID ID 23](#_Toc181199855)

[13. REFERENCES 25](#_Toc181199856)

[14. APPENDICES 27](#_Toc181199857)

[14.1. AGREE II User Manual 27](#_Toc181199858)

[14.2. GRADE System for Assessing Evidence 29](#_Toc181199859)

[14.3. Search Strategies 34](#_Toc181199860)

[14.4. Equality Impact Assessment Table 36](#_Toc181199861)

[14.5. Pilot Feedback Form 39](#_Toc181199862)

1. ABSTRACT

This guideline provides evidence-based recommendations for the use of doxycycline post exposure prophylaxis (doxyPEP) for the prevention of syphilis. DoxyPEP should be part of a comprehensive approach to the prevention of STIs, along with condom use, appropriate HIV prevention interventions, vaccination, STI testing, treatment and management, and appropriate risk reduction advice and psychological interventions if indicated.

**Keywords:** Doxycycline, post-exposure prophylaxis, chlamydia, syphilis, gonorrhoea, STI prevention, antimicrobial resistance.

1. ABBREVIATIONS

|  |  |
| --- | --- |
| **AE** | Adverse event |
| **AGREE** | Appraisal of Guidelines, Research and Evaluation |
| **AMR** | Antimicrobial resistance |
| **BASHH** | British Association for Sexual Health and HIV |
| **BBV** | Blood‑borne virus |
| **BHIVA** | British HIV Association |
| **CEG** | Clinical Effectiveness Group |
| **CI** | Confidence interval |
| **DoxyPEP** | Doxycycline post-exposure prophylaxis |
| **GBMSM** | Gay, bisexual, and other men who have sex with men |
| **GUM** | Genitourinary medicine |
| **GPP** | Good practice point |
| **GRADE** | Grading of Recommendations, Assessment, Development, and Evaluations |
| **HR** | Hazard ratio |
| **HIV** | Human immunodeficiency virus |
| **HPV** | Human papillomavirus |
| **INR** | International normalised ratio |
| **LGV** | Lymphogranuloma venereum |
| **NAAT** | Nucleic acid amplification test |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Care Excellence |
| **PrEP** | Pre-exposure prophylaxis |
| **RCT** | Randomised clinical trials |
| **SAE** | Serious adverse event |
| **STI**  **TGW** | Sexually transmitted infection  Transgender women |
| **UK** | United Kingdom |
| **UKHSA**  **vs.** | UK Health Security Agency  Versus |
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1. SUMMARY OF RECOMMENDATIONS

|  |  |  |
| --- | --- | --- |
| **Ref (Section, page)** | **Recommendation** | **GRADE** |
| 1 (Section 8.1, p15) | We recommend doxyPEP for cisgender GBMSM and TGW at elevated risk of acquiring syphilis. | 1A |
| 2 (Section 8.1, p15) | DoxyPEP may be appropriate, and therefore considered, for other TGW and cisgender men at risk of STIs or to help mitigate the potential risk of transmitting infection to cisgender female and other partners with a womb and ovaries. | 1D |
| 3 (Section 8.2.1, p16) | We recommend taking 200 mg of doxycycline, within 24 hours and no later than 72 hours after sex. | 1A |
| 4 (Section 8.2.3, p17) | Regarding user education and support, we recommend:   1. Providing clear information on dosing and timing, including infographics; 2. Offering clear guidance on current unknowns and limits of the evidence base, and addressing individuals’ concerns about AMR and doxycycline use; 3. Informing users about potential side effects, including photosensitivity, headache, nausea, vomiting, dyspepsia, and rash. | 1D |
| 5 (Section 9.1.1, p18) | We recommend that STI testing should be undertaken consistent with current BASHH guidelines. | 1D |
| 6 (Section 9.1.1, p18) | We recommend STI treatment and management of incident infections should be in accordance with current BASHH guidelines. | 1D |
| 7 (Section 9.1.1, p18) | We recommend offering doxyPEP users who are contacts of syphilis epidemiological treatment in line with current BASHH guidelines due to the long potential time between exposure and reliably ruling out infection by serology. | 1D |
| 8 (Section 9.1.1, p18) | We recommend that asymptomatic doxyPEP users who are contacts of chlamydia and took doxyPEP within 72 hours of exposure, do not require epidemiological treatment. If the individual attends within 72 hours of exposure but has not yet taken doxyPEP, then consider taking a dose of doxyPEP instead of offering standard epidemiological treatment (i.e., seven days of doxycycline). If the individual is in the clinical service then consider offering a test for chlamydia. | 2D |
| 9 (Section 9.1.1, p18) | We recommend that asymptomatic doxyPEP users who are contacts of gonorrhoea or *Mycoplasma genitalium* should be managed according to the relevant BASHH guideline. | 1D |
| 10 (Section 9.1.2, p19) | We recommend reporting of doxyPEP use for public health surveillance purposes according to the requirements of the relevant UK nation. | 1D |

AMR = Antimicrobial resistance; BASHH = British Association for Sexual Health and HIV; DoxyPEP = Doxycycline post‑exposure prophylaxis; GBMSM = Gay, bisexual, and other men who have sex with men; Ref = Reference; STI = Sexually transmitted infection; TGW = Transgender women; UK = United Kingdom; UKHSA = UK Health Security Agency.

1. INTRODUCTION AND METHODOLOGY
   1. Objectives

This guideline provides evidence-based recommendations for the use of doxycycline post‑exposure prophylaxis (doxyPEP) for the prevention of Syphilis. It is written for use by healthcare professionals working within specialist (level 3) sexual health services in the United Kingdom (UK), providing care tailored for patients aged 16 years and older.

* 1. Search strategy

This guideline was produced according to specifications set out in the British Association for Sexual Health and HIV (BASHH) Clinical Effectiveness Group (CEG) document ‘framework for guideline development and assessment’ (2015, updated 2019) accessed at <https://www.bashhguidelines.org/media/1229/2015-guidelines-framework-amended-dec-2019.pdf>.

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system was used to assess the evidence and make recommendations as detailed in Appendix 14.2.

A search of published articles between 01 Jan 1990 to 09 Feb 2024 was conducted in PUBMED to address two primary questions:

1. Does taking doxycycline after having condomless vaginal, anal or oral sex reduce bacterial sexually transmitted infections (STIs) compared to not taking it?
2. What are the risks of using doxycycline, including antimicrobial resistance and side effects such as dermatological, gastrointestinal, and metabolic issues?

Search strategies and inclusion/exclusion criteria for assessing doxycycline’s efficacy and safety are provided in Appendix 14.3.

* 1. Methods

Article titles and abstracts were reviewed and if relevant the full text article was obtained. Abstracts from meetings in the relevant period were hand-searched and considered. Priority was given to randomised controlled trials and systematic review evidence, and recommendations were made and graded based on the best available evidence (Appendix 14.2).

* 1. Equality impact assessment

An assessment of the guideline and its recommendations was undertaken to ensure the principles of equality and diversity were adhered to and is available in Appendix 14.4.

BASHH has adopted an anatomical approach without assuming gender in the majority of guidelines and uses gender terminology in line with BASHH ‘sexual health standards for trans, including non-binary, people’.

* 1. Stakeholder involvement, piloting, and feedback

The first draft was produced by the multi-professional and multidisciplinary writing group and then submitted to the BASHH CEG for review using the AGREE appraisal tool (Appendix 14.1). The second draft was posted on the BASHH website for consultation (2 months), with the authors responsible for assessing feedback. The document was also reviewed by a patient representative, target users, and the public panel of BASHH, and their feedback was considered by the authors and used to inform the final version. Appropriate input was also sought from national antimicrobial resistance (AMR) experts and NHS England colleagues involved in doxycycline drug procurement, stock and supply chains. The final draft was presented to the CEG for review and piloting in sexual health clinics. Maintaining the guidelines is the responsibility of BASHH CEG.

Once the guideline is published, the CEG will keep it under review should critical new evidence become available that affects the current recommendations. The guideline will be formally reviewed and updated, if necessary, every five years.

1. EFFICACY

Four randomised controlled trials of doxyPEP to reduce bacterial STIs were assessed. In each trial, participants were randomised to receive an oral dose of 200 mg doxycycline within 72 hours of condomless sex, or to receive standard care (i.e., routine STI testing and no doxycycline). Three studies were conducted among gay, bisexual, and other men who have sex with men (GBMSM) and transgender women (TGW) using human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) ([Molina et al., 2024](#_ENREF_14); [Molina et al., 2018](#_ENREF_15)), or either using HIV PrEP or living with HIV ([Luetkemeyer et al., 2023](#_ENREF_12)). One study involved cisgender women using HIV PrEP ([Stewart et al., 2023](#_ENREF_20)). The studies involving GBMSM and TGW showed that doxyPEP effectively prevented chlamydia and syphilis infections, although there was no consensus on the effectiveness of doxyPEP in reducing incidence of gonorrhoea infections. The study involving cisgender women did not find an effect of doxyPEP on reducing the incidence of bacterial STIs.

GBMSM and TGW: A sub study of IPERGAY included 232 participants using HIV PrEP ([Molina et al., 2018](#_ENREF_15)). Participants randomised to doxyPEP (n=116) showed a reduction in chlamydia (hazard ratio [HR]=0.30; 95% confidence interval [CI]=0.13–0.70) and syphilis (HR=0.27; 0.07–0.98), but no statistically different reduction in gonorrhoea (HR=0.83; 0.47–1.47). There was no impact on the incidence of *Mycoplasma genitalium* ([Bercot et al., 2021](#_ENREF_2)). The DoxyPEP study included 501 participants using HIV PrEP or living with HIV ([Luetkemeyer et al., 2023](#_ENREF_12)). Participants randomised to doxyPEP (n=339) experienced significant reductions in chlamydia for both HIV PrEP users (relative risk [RR]=0.12; 95% CI=0.05–0.25) and those living with HIV (RR=0.26; 0.12–0.57). Similar reductions were observed for syphilis (RR=0.13; 0.03–0.59 for HIV PrEP users and RR=0.23; 0.04–1.29 for those living with HIV). For gonorrhoea, there was a lesser but statistically significant reduction (RR=0.45; 0.32–0.65 for HIV PrEP users and RR=0.43; 0.26–0.71 for those living with HIV). The DOXYVAC study included 556 participants using PrEP and also randomised participants to receive the 4CMenB meningococcal vaccination ([Molina et al., 2024](#_ENREF_14)). In keeping with the other studies, doxyPEP significantly reduced chlamydia (adjusted HR [aHR]=0.14; 0.09–0.23) and syphilis diagnoses (aHR=0.21; 0.11–0.41) but was less effective for gonorrhoea (aHR=0.67; 0.52–0.87). Overall, these results provide clear evidence of the efficacy of doxyPEP in reducing chlamydia and syphilis in GBMSM and TGW compared to standard care, with a lesser or no effect on gonorrhoea, likely impacted by tetracycline resistance in *Neisseria gonorrhoeae*.

Similar reductions to those seen in the clinical trials have been observed following real-world implementation of doxyPEP. Among the 39% of 3081 HIV PrEP users who took up doxyPEP in one clinic in San Francisco, there was a significant decline in new chlamydia and syphilis diagnoses in the first six months of use (incidence rate ratio [IRR]=0.33; 0.23–0.46 and IRR=0.22; 0.07–0.54, respectively) ([Scott et al., 2024](#_ENREF_19)). In the first year of implementation in San Francisco, approximately 20% of GBMSM and TGW attending public sexual health clinics (3974 individuals) initiated doxyPEP with a decline of 51% (95% CI=43-58%) in early syphilis notifications and 50% (95%CI=38-59%) in chlamydia observed ([Sankaran et al., 2024](#_ENREF_18)). In a Northern California health insurance cohort, including San Francisco, 2,253 out of 11,551 HIV PrEP users were dispensed doxyPEP, with median monthly usage of 6.5 doses. Significant declines in STIs were observed, including a 79% reduction in chlamydia (95%CI=73-83%) and an 80% reduction in syphilis(95%CI=63-98%). Smaller reductions were noted in urethral and rectal gonorrhoea diagnoses, though no significant change was observed in pharyngeal gonorrhoea ([Traeger et al., 2025](#_ENREF_23)).

Cisgender women: The dPEP Kenya study included 449 cisgender women using HIV PrEP ([Stewart et al., 2023](#_ENREF_20)). The results showed no significant effect of doxyPEP (n=224) in reducing STIs compared to standard care (RR=0.88; 0.60–1.29). Subsequent analyses have found poor adherence to doxyPEP among participants which may be the reason for a lack of observed effectiveness. In a small pharmacokinetic study including nine women given a single 200 mg dose of doxycycline, high concentrations of doxycycline in vaginal tissue were achieved, suggesting it could be effective at preventing infection ([Haaland et al., 2024](#_ENREF_9)). However, at the time of writing, empirical data to show efficacy of doxyPEP to prevent incident bacterial STIs among cisgender women is lacking.

**Other potential benefits of doxyPEP**

Whilst most studies have focussed on the efficacy of reducing infection acquisition, there are also potential quality of life benefits associated with doxyPEP use. Participants of the DoxyPEP study reported benefits to their quality of life and mental health by reducing anxiety about acquiring and transmitting STIs and by providing more control over their sexual health ([Fredericksen et al., 2024](#_ENREF_8)).

1. SAFETY
   1. Safety and tolerability evidence from randomised clinical trials

In the four randomised clinical trials described in section 6, doxycycline was safe and well‑tolerated. There were few or no discontinuations and serious adverse events (SAEs). In the IPERGAY sub study, there was no statistical difference in adverse events (AEs) between doxyPEP and control arms except for drug‑related gastrointestinal effects (25% versus [vs.] 14%,p=0.03), and 10 of 116 participants discontinued ([Molina et al., 2018](#_ENREF_15)). In the DoxyPEP study, no SAEs attributable to doxycycline and a low occurrence of diarrhoea and headache were observed, and 2% of 339 participants discontinued because of unacceptable side effects or patient preference ([Luetkemeyer et al., 2023](#_ENREF_12)). In the DOXYVAC study, a single SAE related to doxycycline was reported (a fixed drug eruption) amongst 369 GBMSM, and six participants among the doxyPEP users discontinued the study, all due to GI side effects ([Molina et al., 2024](#_ENREF_14)). Lastly, in the doxyPEP Kenya study, there were no SAEs related to doxycycline reported among 224 cisgender women, and 10 participants among the doxyPEP users discontinued the study ([Stewart et al., 2023](#_ENREF_20)).

* 1. Side effects

The most common side effects of long-term doxycycline include gastrointestinal symptoms (e.g., nausea, vomiting, dyspepsia) and photosensitivity. Rare side effects associated with long-term use of doxycycline include benign intracranial hypertension, and liver-related toxicity ([Digre, 2003](#_ENREF_6); [*Doxycycline 100 mg capsules - the summary of product characteristics and the patient information leaflet. Sovereign Medical. Last updated 20 June 2024.*](#_ENREF_7)).

* 1. Long‑term safety

A systematic review and meta‑analysis of 67 studies of long‑term doxycycline use (i.e. >8 weeks), published between August 2003 and January 2023, found no difference in SAEs between the doxycycline and placebo groups ([Chan et al., 2023](#_ENREF_4)). Discontinuations due to doxycycline related AEs were rare. However, gastrointestinal (nausea, vomiting, abdominal pain), dermatologic symptoms (photosensitivity), and neurological symptoms (headache and dizziness) symptoms were more likely among those taking doxycycline compared to those who were not.

* 1. Antimicrobial resistance

The main concern about using doxycycline prophylaxis is in relation to AMR in sexually and non-sexually transmitted infections. The most difficult, but potentially most significant, risk to quantify is selection of resistance amongst potentially pathogenic bacterial flora such as *Staphylococcus aureus* and respiratory tract pathogens. Doxycycline is a first-line antibiotic for both community and hospitalised patients with skin and soft tissue infections and respiratory tract infections.

We emphasise the importance of considering the risk of AMR at both individual and population levels, following the National Institute for Health and Care Excellence (NICE) guideline on long‑term prophylactic antibiotic use (e.g., uncomplicated lower urinary tract infection, bronchiectasis, and acne). Clinical trials evaluating doxyPEP have reported varying levels of tetracycline resistance evolution in *N. gonorrhoeae*, commensal *Neisseria* species, and the gut microbiome associated with doxyPEP use. However, resistance to doxycycline has not been observed in *Treponema pallidum* and *Chlamydia trachomatis*. In a recent in-vitro study, *T. pallidum* did not develop tetracycline-resistance following long-term sub-bactericidal exposure to doxycycline ([Tantalo et al., 2024](#_ENREF_22)).

In the DoxyPEP study, doxycycline-resistant *N. gonorrhoeae* isolates increased from 28.6% at baseline to 38.5% in doxyPEP users, although the number of isolates available for testing was low (7 at baseline, 13 during follow‑up) ([Luetkemeyer et al., 2023](#_ENREF_12)). Doxycycline resistance in *Staphylococcus aureus* isolated from the oro- and nasopharynx increased from 8.6% at baseline to 21.6% at 6 months and 16.1% at 12 months, although overall rates of carriage fell ([Luetkemeyer et al., 2023](#_ENREF_12)). DoxyPEP use was associated with an increased expression of molecular markers of tetracycline resistance within the gut microbiome of users but did not significantly alter gut microbiome diversity or composition ([Chu et al., 2024](#_ENREF_5)). In the DOXYVAC study, tetracycline‑resistant *N. gonorrhoeae* was significantly higher in the doxyPEP group compared to the standard care group (35.5% vs. 12.5%; p=0.043) ([Molina et al., 2024](#_ENREF_14)). The dPEP Kenya study reported 100% prevalence of tetracycline resistance in *N. gonorrhoeae* at baseline and all follow-up points in both arms ([Stewart et al., 2023](#_ENREF_20)).

No phenotypic or genotypic markers of doxycycline resistance in chlamydia diagnosed among doxyPEP users were detected in any of the RCTs where this was explored ([Molina et al., 2024](#_ENREF_14); [Molina et al., 2018](#_ENREF_15); [Stewart et al., 2023](#_ENREF_20)). In the IPERGAY substudy, 12.5% of *Mycoplasma genitalium* isolates had the MG 16S rRNA mutation although its association with tetracycline resistance is not understood (Bercot 2021). None of the studies explored resistance in *T. pallidum* or sexually transmitted enteric infections.

Published studies on long-term doxycycline use for acne have not demonstrated increased resistance to doxycycline in *Staphylococcus epidermidis*, however, long-term use generally led to higher rates of AMR emergence in *Cutibacterium acnes* (previously *Propionibacterium acnes*) ([Legiawati et al., 2023](#_ENREF_10); [Moon et al., 2012](#_ENREF_16); [Nakase et al., 2022](#_ENREF_17); [Tan et al., 2001](#_ENREF_21)). Military studies on doxycycline for malaria prophylaxis found no difference in extended beta lactamase‑producing Enterobacteriaceae and no significant increase in resistance to doxycycline in *Campylobacter* and enterotoxigenic *Eschericia coli* (ETEC), although higher rates of tetracycline‑resistant non-ETEC *E.coli* was seen ([Arthur et al., 1990](#_ENREF_1); [Buchek et al., 2021](#_ENREF_3)). Additionally, AMR emergence in *S. aureus* related to history of daily doxycycline use has been observed ([Lesens et al., 2007](#_ENREF_11); [Mende et al., 2016](#_ENREF_13)). Overall, these studies provided limited understanding of doxycycline’s impact on AMR in STI and non-STI cases due to small sample size and varied study designs.

1. BASELINE ASSESSMENT
   1. Considerations for doxyPEP use across different populations

Current evidence consistently demonstrates that doxyPEP is effective at reducing the incidence of chlamydia and syphilis among GBMSM and TGW. In the UK, doxyPEP is not expected to be effective in preventing gonorrhoea due to the high prevalence of tetracycline resistance.

Since most chlamydial infections among GBMSM and TGW are not associated with harmful clinical manifestations or sequelae, the major physical health benefit of doxyPEP in these key populations is likely the prevention of syphilis. The impact of doxyPEP on incident infection with Lymphogranuloma venereum (LGV) has not been reported in randomised clinical trials (RCTs).

We recommend doxyPEP for cisgender GBMSM and TGW at elevated risk of acquiring syphilis (GRADE 1A). Syphilis risk may be associated with a recent (in the last year) of a bacterial STI diagnosis and a recent history (in the last 3 months) of multiple new, occasional, or one-off sexual partners, including reporting group-sex and chemsex.

We recognise that chlamydia and syphilis may pose additional potential harms to people with a womb and ovaries (i.e., cisgender women, transgender men, and non-binary people assigned female at birth) through adverse reproductive health sequelae and vertical transmission. Therefore, whilst there is no empirical evidence to support prescribing doxyPEP to people with a womb and ovaries, we recommend considering doxyPEP for GBMSM and TGW with concurrent male and cisgender female or other partners with a womb and ovaries (GRADE 1D). Currently there is insufficient evidence to support a recommendation for the use of doxycycline 200mg within 72 hours of receptive vaginal sex. Furthermore, whilst available data suggests good protection in cisgender men and transgender women engaging in oral and anal sex, it is not yet known whether this intervention protects from infection and potential sequalae (for example, pelvic inflammatory diseases and congenital syphilis) in cisgender women, transgender men and other individuals with a vagina who only engage in oral and/or anal sex.

* 1. Health equity considerations

There is currently insufficient evidence of effectiveness to recommend doxyPEP in cisgender women and other people with a womb and ovaries, transgender men and people assigned female at birth. Because of these uncertainties, the balance of risk, particularly the development, and individual and public health consequences of antimicrobial resistance, and benefit may not support prescribing doxyPEP to people in whom effectiveness has not yet been demonstrated. This will be reviewed and updated as new evidence emerges. In addition, for cisgender GBMSM and TGW, where the use of doxyPEP is supported by RCT evidence, some individuals may be less likely to access or face additional barriers to accessing existing sexual health services. Services should try to mitigate issues of inequity of access and uptake for cisgender GBMSM and TGW where there is evidence to support the use of doxyPEP.

* + 1. Dosage and administration

We recommend taking 200 mg of doxycycline, within 24 hours and no later than 72 hours after sex (GRADE 1A). No more than 200 mg of doxycycline should be taken in each 24‑hour period (i.e., maximum of 200 mg of doxycycline every 24 hours).

There is no evidence to guide whether the effectiveness of doxyPEP varies depending on when it is taken in the 72-hour period after sex. However, individuals may have concerns about taking frequent antibiotics or experience side effects meaning they wish to reduce the frequency of taking doxycycline. Acknowledging this lack of evidence, individuals having sex on more than one occasion over a 72-hour period may consider taking a single 200 mg dose of doxycycline at the end of the 72‑hour period, rather than multiple doses, to cover the entire period of risk (GRADE 2D).

There is no evidence to guide the optimal number of tablets to prescribe. This should be agreed following discussion with the patient, taking into consideration anticipated doxyPEP consumption and patient wishes. Prescribers should consider the potential service and patient impact of prescribing too few tablets to cover the period between service contacts, including scheduling of PrEP and three-monthly STI checks.

* + 1. Baseline screening and diagnostic

The provision of doxyPEP should be part of a holistic and comprehensive sexual health approach, including STI, HIV and blood‑borne virus (BBV) testing, vaccination and other risk reduction strategies if appropriate like motivational interviewing in line with current national clinical standards and guidelines. HIV negative individuals on doxyPEP should be assessed for eligibility for HIV PrEP and informed about HIV PEP and how to access this. HIV positive individuals on doxyPEP should be managed according to relevant British HIV Association (BHIVA) guidelines.

We do not recommend any additional renal or liver monitoring specific to doxyPEP use alone.

* + 1. User education and support

Regarding user education and support, we recommend (GRADE 1D):

1. Providing clear information on dosing and timing, including infographics;
2. Providing clear information on the potential benefits and harms of taking doxyPEP including the current unknowns and limits of the evidence base and addressing any concerns an individual has about AMR and doxycycline use;
3. Informing users about potential side effects, including photosensitivity, headache, nausea, vomiting, dyspepsia, and rash, and potential strategies to limit these, for example, taking doxycycline with a big glass of water and some food, remaining upright for 30 minutes after taking a dose of doxyPEP, avoiding sunbeds and wear sunscreen with SPF
4. Supporting doxyPEP users to make informed decisions about when and how to use doxyPEP including information about alternatives to doxyPEP (e.g., condoms);
5. Providing clear information that doxyPEP is not 100% effective at preventing acquisition of bacterial STIs and that individuals should promptly seek clinical advice if they develop signs or symptoms of an STI. Individuals should be advised to undertake STI testing at a frequency consistent with current BASHH guidelines;
6. Informing users about possible drug‑drug interactions, such as avoiding taking the doxycycline at the same time as antacids containing aluminium, calcium, magnesium and other cations (separate doses by at least 2 hours). Additionally, note the possibility for increased clearance of doxycycline in patients taking carbamazepine or phenytoin, and advise against using it if they are on ciclosporin or isotretinoin;
7. Informing users that long-term alcohol consumption may decrease the effectiveness of doxycycline.
8. MONITORING AND FOLLOW-UP
   * 1. Follow-up and monitoring

There is insufficient evidence to recommend any change to the STI testing method or frequency in individuals taking doxyPEP. We recommend that STI testing should be undertaken consistent with current BASHH guidelines (GRADE 1D).

The effect on serological response to syphilis infection is not known. We recommend that syphilis testing and treatment should be offered consistent with current BASHH guidelines (GRADE 1D).

There is insufficient evidence to recommend any change to the management of incident STIs diagnosed among doxyPEP users. We recommend STI treatment and management of incident STIs, should be in accordance with current BASHH guidelines. (GRADE 1D).

The impact of doxyPEP on the need for treating contacts of syphilis and chlamydia is not known. We recommend offering epidemiological treatment to doxyPEP users who are contacts of syphilis, in line with current BASHH guidelines due to the long potential time between exposure and reliably ruling out infection by serology (GRADE 1D). We recommend that asymptomatic doxyPEP users who are contacts of chlamydia and took doxyPEP within 72 hours of exposure, do not require epidemiological treatment (GRADE 2D). If the individual attends within 72 hours of exposure but has not yet taken doxyPEP, then consider taking a dose of doxyPEP instead of offering standard epidemiological treatment (i.e., seven days of doxycycline) (GRADE 2D). If the individual is in the clinical service, then consider offering a test for chlamydia (GRADE 2D). We recommend that asymptomatic doxyPEP users who are contacts of gonorrhoea, mycoplasma or LGV are managed according to the relevant current BASHH guideline (GRADE 1D).

We do not currently recommend additional monitoring of individuals using doxyPEP to address concerns about the impact of doxyPEP use on AMR in either sexually or non‑sexually transmitted infections. However, if a situation arises that requires additional monitoring, we recommend implementing monitoring and surveillance processes that prioritise health equity, including the minimising of potential barriers to access. These processes should be developed in collaboration with and through engagement with communities using doxyPEP or those who might benefit from doxyPEP use.

* + 1. Coding and data collection

We recommend reporting of doxyPEP use for public health surveillance purposes according to the requirements of the relevant UK nation (GRADE 1D). This will allow for easier monitoring and evaluation in relation to the uptake and use of doxyPEP, the incidence of STIs among users and any associations with AMR.

* 1. Recommendations for non-specialist providers

Given the widespread availability, low cost, and high effectiveness of doxycycline in averting incident infections with chlamydia and syphilis, doxyPEP might be prescribed, continued and perhaps initiated in other settings although these models of care have not been described in the UK. Recommendations in this guideline should be followed regardless of where doxyPEP is provided.

1. AUDITABLE OUTCOME MEASURES
2. RECOMMENDATIONS FOR FUTURE RESEARCH
   1. Implementation and impact

* What is the efficacy of doxyPEP in cisgender women, transgender men, and other people having vaginal/frontal sex?
* What is the acceptability, barriers, and facilitators to doxyPEP use among key population groups?
* What are the optimal models of doxyPEP delivery and implementation to support acceptability and use among key populations?
* How does doxyPEP impact population‑level STI rates, including rates among key population groups (e.g. young people, GBMSM, transgender and non‑binary individuals, and racially minoritised groups) and non-doxyPEP users, particularly in relation to including congenital syphilis?
* What are the patterns of antibiotic use among high‑use populations when considering doxyPEP?
* What are the motivations and decision‑making processes among populations using doxyPEP?
* What is the frequency and pattern of doxyPEP use in relation to different sexual partner types?
* How does doxyPEP use affect the interpretation of syphilis serology in individuals who acquire syphilis whilst using doxyPEP?
* What role does the timing, partners, frequency, and type of sexual activity play in syphilis positivity among doxyPEP users, and how do these factors influence recommendations for testing and epidemiological treatment?
* How does doxyPEP use influence sexual behaviour, sexual freedom, and sexual pleasure among users?
* What is the cost-effectiveness and potential cost-saving impact of doxyPEP use in various populations?
* What are the optimal dosing regimens for doxyPEP, and how do maximum dosing intervals (e.g. every 24 hours vs. every 72 hours) impact its effectiveness and safety?
  1. Antimicrobial resistance and monitoring
* How do socioeconomic and demographic factors influence access to and use of doxyPEP, and what are the barriers to inclusion for marginalised populations in its preventive use?
* What is the impact of doxyPEP use on antimicrobial resistance in *S. aureus* and *Streptococcus?*
* What is the optimal modality, frequency, and targets for antimicrobial resistance surveillance in bacterial STIs and important non-STIs as a result of doxyPEP use?
* What is the impact of doxyPEP use on human microbiome composition and resistance?
* What is the impact of doxyPEP use on antimicrobial resistance in *N. gonorrhoeae*, commensal *Neisseria* species, *T. pallidum*, *C. trachomatis* and other STIs?

1. DISCLOSURES
   1. Acknowledgements

The authors would like to thank Sarah Alexander (UKHSA), Diane Ashiru-Oredupe (UKHSA), Colin Brown (UKHSA), Michelle Cole (UKHSA), Ryan Hamilton (British Society for Antimicrobial Chemotherapy), Dakshina Jeyaratnam (UKHSA), Rajeka Lazarus (British Infection Association), Tashlyn Nyoni (UKHSA), Rachel Pitt (UKHSA), Laura Whitney (NHS England), members of the BASHH CEG. Medical writing assistance was provided by Gökçe Ayan (Veristat).

* 1. Declaration of Conflicting Interests

All members of the guideline writing committee completed the BASHH conflict of interest declaration and submitted it to the CEG. No authors had any relevant conflicts of interest to declare, and the content of the guideline is not attributed to any organisation they are associated with.

* 1. Funding

The authors received no financial support for the research, authorship, and/or publication of this guideline.

* 1. Editorial Independence

This guideline was commissioned, edited, and endorsed by the BASHH CEG without external funding being sought or obtained. All members of the guideline writing committee completed the BASHH conflicts of interest declaration detailed below at the time the guideline’s final draft was submitted to the CEG.

* 1. Membership of the Clinical Effectiveness Group

Current membership of the BASHH Clinical Effectiveness Group is available at [www.bashh.org/bashh-groups/clinical-effectiveness-group/](http://www.bashh.org/bashh-groups/clinical-effectiveness-group/).

* 1. ORCID ID

John Saunders: <https://orcid.org/0000-0003-3020-9916>

Dwayne-Wilson Hunt: <https://orcid.org/0000-0002-1275-3531>

Hamish Mohammed: <https://orcid.org/0000-0002-2060-7286>

John Gilmore: <https://orcid.org/0000-0002-3943-0724>

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1. APPENDICES
   1. AGREE II User Manual

The AGREE II consists of 23 key items organised within 6 domains followed by 2 global rating items (“Overall Assessment”). Each domain captures a unique dimension of guideline quality [[1]](#footnote-2).

**DOMAIN 1.** SCOPE AND PURPOSE

**1.** The overall objective(s) of the guideline is (are) specifically described.

**2.** The health question(s) covered by the guideline is (are) specifically described.

**3.** The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

**DOMAIN 2.** STAKEHOLDER INVOLVEMENT

**4.** The guideline development group includes individuals from all relevant professional groups.

**5.** The views and preferences of the target population (patients, public, etc.) have been sought.

**6.** The target users of the guideline are clearly defined.

**DOMAIN 3.** RIGOUR OF DEVELOPMENT

**7.** Systematic methods were used to search for evidence.

**8.** The criteria for selecting the evidence are clearly described.

**9.** The strengths and limitations of the body of evidence are clearly described.

**10.** The methods for formulating the recommendations are clearly described.

**11.** The health benefits, side effects, and risks have been considered in formulating the recommendations.

**12.** There is an explicit link between the recommendations and the supporting evidence.

**13.** The guideline has been externally reviewed by experts prior to its publication.

**14.** A procedure for updating the guideline is provided.

**DOMAIN 4.** CLARITY OF PRESENTATION

**15.** The recommendations are specific and unambiguous.

**16.** The different options for management of the condition or health issue are clearly presented.

**17.** Key recommendations are easily identifiable.

**DOMAIN 5.** APPLICABILITY

**18.** The guideline describes facilitators and barriers to its application.

**19.** The guideline provides advice and/or tools on how the recommendations can be put into practice.

**20.** The potential resource implications of applying the recommendations have been considered.

**21.** The guideline presents monitoring and/or auditing criteria.

**DOMAIN 6.** EDITORIAL INDEPENDENCE

**22.** The views of the funding body have not influenced the content of the guideline.

**23.** Competing interests of guideline development group members have been recorded and addressed.

* 1. GRADE System for Assessing Evidence

**Introduction:**

There has been a general move to using the GRADE system by many guideline producing bodies in recent years and the BMJ published a series of papers about the method in 2008 [[2]](#footnote-3),[[3]](#footnote-4),[[4]](#footnote-5),[[5]](#footnote-6),[[6]](#footnote-7),[[7]](#footnote-8).

The GRADE system applied in its purest form requires scientific analyses of evidence to produce “tables” from a series of “PICO” questions: Questions that identify the patient problem or population (P), intervention (I) (or aetiology/diagnosis/frequency/prognosis), comparison (C) and outcome(s) (O). Practically this is very labour intensive and requires someone very experienced in this area, and many large guideline writing bodies employ a scientist to do this for them. However, some bodies adapt the GRADE system according to their own needs, assess the evidence in the way they have done in the past, and then make strengths of recommendations according to the GRADE system, which when applied in this way is quite simple to do and understand. BASHH have adopted GRADE to use in this manner.

**The principles of GRADE:**

1. Assessment of the evidence

GRADE offers four levels of evidence quality: high, moderate, low, and very low, with randomised trials classed as high-quality evidence and observational studies as low-quality evidence. Quality may be downgraded because of limitations in study design or implementation, imprecision of estimates (wide confidence intervals), variability in results, indirectness of evidence, or publication bias. Quality may be upgraded because of a very large magnitude of effect, a dose-response gradient, and if all plausible biases would reduce an apparent treatment effect.

Summary of factors affecting quality of evidence:

|  |  |  |
| --- | --- | --- |
| Study limitations | Imprecision | Large magnitude of effect |
| Inconsistency of results | Publication bias | Dose-response gradient |
| Indirectness of evidence | Factors that might increase quality of evidence | Plausible confounding, which would reduce a demonstrated effect |

Based on the analysis of the evidence with these factors borne in mind the evidence should be graded as follows:

|  |  |
| --- | --- |
| **A** | A body of evidence of high-quality meta-analyses, systematic reviews of and RCTs directly applicable to the target population |
| **B** | As above but relating to high quality case control or cohort studies with low risk of bias or confounding and high probability that a relationship is causal |
| **C** | As B but trials may have some flaws |
| **D** | Non-analytic evidence (e.g., case reports or series or expert opinion) |

However, when reviewing evidence graded A-D as above the grading can be altered follows:

* + The strength of recommendation should be higher if the following apply:
    - A large effect of an intervention is demonstrated.
    - Dose response/evidence of gradient.
    - All plausible confounding would reduce a demonstrated effect or would suggest a spurious effect when results show no effect.
* Lower if there is evidence of:
  + - Serious/very serious study limitations
    - Inconsistency
    - Indirectness
    - Imprecision
    - Publication bias
    - Study limitations
    - Inconsistency of results
    - Indirectness of evidence
    - Imprecision
    - Publication bias

1. Formulating recommendations

There are only two strengths of recommendation, which may be either for or against an intervention: 1 = strong or 2 = weak. Pragmatically, this means the following:

* Strong recommendation for intervention:

For patients — Most people in this situation would want the recommended course of action and only a small proportion would not.

For clinicians — Most people should receive the intervention.

For quality monitors — Adherence to this recommendation could be used as a quality criterion or performance indicator. If clinicians choose not to follow such a recommendation, they should document their rationale.

* Weak recommendation for intervention:

For patients — Most people in this situation would want the suggested course of action, but many would not.

For clinicians — Examine the evidence or a summary of the evidence yourself and be prepared to discuss that evidence with patients, as well as their values and preferences.

For quality monitors — Clinicians’ discussion or consideration of the pros and cons of the intervention, and their documentation of the discussion, could be used as a quality criterion.

* No specific recommendation:
  + The advantages and disadvantages are equivalent.
  + The target population has not been identified.
  + Insufficient evidence on which to formulate a recommendation.

1. Consideration of using PICO

This may be helpful if guideline writing committee wish to utilise this method, this is explained in the NICE guideline manual; chapter 4:6.

|  |  |
| --- | --- |
| **Patients/population** | Which patients or population of patients are we interested in? How can they be best described? Are there subgroups that need to be considered? |
| **Intervention** | Which intervention, treatment or approach should be used? |
| **Comparison** | What is/are the main alternative/s to compare with the intervention? |
| **Outcome** | What is really important for the patient? Which outcomes should be considered, such as intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning? Should other measures such as quality of life, general health status and costs be considered? |

1. Consideration of costs

These may or may not legitimately be included in the GRADE system, but it would be sensible in the current climate to always consider these, and if they are not considered this should be stated and why – for example, there is no significant difference in cost between the recommended treatments.

Generally speaking, GRADE suggests a balance sheet should inform judgments about whether the net benefits are worth the incremental costs. Evidence profiles should always present resource use, not just monetary values.

1. Using the GRADE grid to resolve differences:

This supports the Delphi technique we already adopt, i.e., to develop a consensus within the group.

1. GRADE training for BASHH guideline authors

Authors need to be familiar and confident in using the GRADE system, and training for this is available as follows:

* The papers from the BMJ series in 2008, as listed in the introduction to this appendix. The articles can be accessed through the grade working group web site at: <http://www.gradeworkinggroup.org/publications/index.htm>
* McMaster GRADE online modules: these have been recommended by the GRADE working group and take about 20 minutes each to complete. The web address is: <http://cebgrade.mcmaster.ca/>
* Journal of Clinical Epidemiology 2011: published a 20-part series that is available through the GRADE working group website (link above).

**Summary:**

BASHH have now moved to the GRADE system for evaluating evidence and making recommendations by asking guideline authors and reviewers to apply the principles outlined in sections 1-3 above. Authors should consider structuring their analysis of evidence into PICO questions addressing Population / Intervention / Comparison / Outcome as stated in section 4. Costs should be included in the evaluation and formulation of recommendations as stated in section 5. When resolution of conflicting opinions is required, the GRADE grid should be used. This appendix is a brief summary of the GRADE system how it is to be adopted by BASHH guideline authors.

* 1. Search Strategies

**Efficacy of doxycycline as PEP to prevent bacterial STIs:**

* Search period for articles: 01‑JAN‑2018 to 27‑JUN‑2024.
* Search terms: (doxycycline) AND (chlamydia OR gonorrhoea OR syphilis) AND (PEP OR post-exposure prophylaxis OR pre-exposure prophylaxis OR PrEP) AND (Clinical Trial[pt]).
* Inclusion criteria: Randomised controlled trials in English, evaluating doxycycline as STI bacterial prophylaxis.
* Exclusion criteria: Non-human or in-vitro studies, unrelated papers, duplicates, unavailable full texts, abstract-only papers, case reports, non-English articles.

**Doxycycline use and adverse events:**

* Search period for articles: 01‑JAN‑1990 to 27-JUN-2024.
* Search terms: “doxycycline” AND (“adverse reaction” OR “adverse event” OR “side effect”).
* Inclusion criteria:Retrospective or prospective clinical study with an average duration of at least 2 months (8 weeks) on doxycycline, with no restrictions set regarding country, publication language, date or patient age, race, gender, or sexuality.
* Exclusion criteria: Non-human or in-vitro studies, unrelated papers, duplicates, unavailable full texts, abstract only papers, case reports, papers reporting doxycycline use in combination with other drugs.
* Review articles from the initial search were reviewed to identify additional studies.

**Doxycycline use and individual level antimicrobial resistance:**

* Search period for articles: 01-JAN‑1990 to 09‑FEB‑2024.
* Search terms: “Long term use AND doxycycline AND antimicrobial resistance”, “Long term use of doxycycline AND antimicrobial resistance”, “Doxycycline resistance AND staphylococcus aureus”, “Doxycycline resistance AND streptococcus pneumoniae”, “Doxycycline resistance AND enteric pathogens”, “Doxycycline resistance AND shigella”, “Doxycycline resistance AND salmonella”, “Doxycycline resistance AND Mycoplasma genitalium”, “Doxycycline resistance AND malaria prophylaxis”, “Doxycycline resistance AND gonorrhoea or Neisseria gonorrhoeae”, “Doxycycline resistance AND chlamydia or chlamydia trachomatis”, “Doxycycline resistance AND treponema pallidum”, “Doxycycline resistance AND syphilis”.
* Inclusion criteria: studies published in English, where the doxycycline dose was at least 100 mg daily, with “long-term” use (either using this term or by documenting doxycycline use was measured in months), and study outcomes included antibiotic susceptibility or resistance of bacteria in the study population.
  1. Equality Impact Assessment Table

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **BASHH Guideline Equality Impact Assessment**  *(based on NICE documentation shared with BASHH August 2019)* | | | | |
| **Guidance title: BASHH Guidelines for the Management** | | **Completed by:** | | **Date:** |
| **How relevant is the topic to equality?** | **Inequalities in health impact of the condition or public health issue** | **Potential of guidance to add value** | **Priority for NHS or other government department** | **Topic relevance; conclusions and outcomes** |
| * Prevalence and impact of condition or public health problem * Prevalence of risk factors | * Inequalities in access, uptake or impact * Timeliness * Equality issues identified by proposers of the topic * Equality issues identified by patient or lay organisations | * Department of Health or other centralised NHS bodies such as NHS England * Local authorities * Home Office * Other agencies | * If equality issues had impact on the guidance summarise these impacts |
| **Sex/gender** |  |  |  |  |
| **Race** |  |  |  |  |
| **Disability** |  |  |  |  |
| **Age** |  |  |  |  |
| **Sexual**  **orientation** |  |  |  |  |
| **Gender reassignment** |  |  |  |  |
| **Religion/belief** |  |  |  |  |
| **Pregnancy & maternity** |  |  |  |  |
| **Other definable characteristics & socioeconomic factors that may affected by protected characteristics, including:**   * Prisoners and young offenders * Refugees and asylum seekers * Migrant workers * Looked after children * Homeless people * Deprivation * Disadvantage associated with geographical distinctions |  |  |  |  |

* 1. Pilot Feedback Form

|  |  |
| --- | --- |
| Guideline |  |
| Dates for the period of guideline piloting |  |
| Name |  |
| Affiliation |  |
| Date |  |
| **Good points about the guideline** |  |
| **Points for improvement** |  |
| **Any other general comments** |  |

1. Appraisal of Guidelines for Research & Evaluation (AGREE) II User Manual, update from December 2017. Access: <https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf> [↑](#footnote-ref-2)
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3. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7651):995-8. [↑](#footnote-ref-4)
4. Schünemann HJ, Oxman AD, Brozek J, et al; GRADE Working Group. BMJ 2008; 336(7653):1106-10. [↑](#footnote-ref-5)
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