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

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2. 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.

3. 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
ETEC	Enterotoxigenic *Escherichia coli*
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
RR	Relative risk
SAE	Serious adverse event
STI	Sexually transmitted infection
TGW	Transgender women
UK	United Kingdom
UKHSA	UK Health Security Agency
vs.	Versus

4. SUMMARY OF RECOMMENDATIONS

Ref (Section, page)	Recommendation	GRADE
1 (Section 9.1, p18)	We recommend doxyPEP for cisgender GBMSM and TGW at elevated risk of acquiring syphilis.	1A
2 (Section 9.1, p18)	We recommend considering doxyPEP for GBMSM and TGW with concurrent male and cisgender female or other partners with a womb and ovaries.	1D
3 (Section 9.1, p19)	Clinicians may consider doxyPEP for people assigned female at birth at elevated risk of acquiring syphilis, on a case-by-case basis, and in discussion with the patient.	2D
4 (Section 9.1, p19)	Clinicians may consider doxyPEP for people at elevated risk of acquiring syphilis attending for clinical care within 72 hours of sexual assault on a case-by-case basis, and in discussion with the patient.	2D
5 (Section 9.2.1, p19)	We recommend taking a single dose of 200 mg (i.e., 2 x 100 mg capsules) of doxycycline, within 24 hours and no later than 72 hours after sex.	1A
6 (Section 9.2.1, p19)	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	2D
7 (Section 9.2.4, p2121)	Regarding user education and support, we recommend: **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 around AMR; **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 plenty of fluid 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), safer sex advice and appropriate behaviour change interventions as outlined in UK national guidance;	1D

	5. Providing clear information that doxyPEP is only for the prevention of syphilis and chlamydia, that it is not 100% effective at preventing acquisition of these infections, that it is unlikely to prevent gonorrhoea, and does not offer protection against any other STIs. 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 doxycycline at the same time as antacids containing aluminium, calcium, magnesium or oral zinc, iron salts or bismuth preparations. Intake of these substances should be separated from dosing with doxycycline as far as possible and 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. The absorption of doxycycline is not notably influenced by the simultaneous ingestion of milk; **7.** Informing users that chronic and heavy alcohol consumption may decrease the effectiveness of doxycycline.	
8 (Section 10.1.1, p22)	We recommend that STI testing should be undertaken consistent with current BASHH guidelines.	1D
9 (Section 10.1.1, p22)	We recommend that doxyPEP users are encouraged to test for asymptomatic STIs at a frequency recommended in BASHH summary guidance on testing for STIs.	1D
10 (Section 10.1.1, p22)	We recommend that syphilis testing and treatment should be offered consistent with current BASHH guidelines	1D
11 (Section 10.1.1, p22)	We recommend STI treatment and management of incident STIs, should be in accordance with current BASHH guidelines.	1D
12 (Section 10.1.1, p22)	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. However, asymptomatic contacts who consistently use doxyPEP following sex or confirm that they took doxyPEP within 72 hours of the potential exposure, may choose not to receive epidemiological treatment, opting for a 'watch and wait' approach instead. We recommend that all contacts of syphilis should be supported to attend if they develop symptoms of potential syphilis infection and have serological testing at appropriate time points.	1D
13 (Section 10.1.1, p22)	We recommend that all contacts of syphilis should be supported to attend if they develop symptoms of potential syphilis infection and have serological testing at appropriate time points	1D

14 (Section 10.1.1, p22)	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. If this test is positive for chlamydia then offer treatment in line with the BASHH guideline on the management of chlamydia.	2D
15 (Section 10.1.1, p22)	We recommend that asymptomatic doxyPEP users who are contacts of gonorrhoea, *M. genitalium* or LGV are managed according to the relevant current BASHH guideline.	1D
16 (Section 10.1.2, p23)	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; LGV = lymphogranuloma venereum; Ref = Reference; SPF = sun protection factor; STI = Sexually transmitted infection; TGW = Transgender women; UK = United Kingdom; UKHSA = UK Health Security Agency.

5. INTRODUCTION AND METHODOLOGY

5.1. 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.

The recommendations may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

5.2. 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 15.2.

A search of published articles between 01 Jan 1990 to 03 April 2025 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 15.3.

5.3. 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 15.2).

5.4. 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 15.4.

BASHH has adopted an anatomical approach without assuming gender in the majority of guidelines and uses gender terminology in line with BASHH recommendations for integrated sexual health services for trans and non-binary people.

5.5. Stakeholder involvement 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 15.1). 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. 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.

6. 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), or living with HIV.[1-3]

One study involved cisgender women using HIV PrEP.[4] The studies involving GBMSM and TGW showed that doxyPEP effectively prevented chlamydia (relative risk [RR]=0.22; 95% confidence interval [CI]=0.13–0.38) and syphilis (RR 0.23; 95% CI=0.13–0.41) infections, although there was no consensus on the effectiveness of doxyPEP in reducing incidence of gonorrhoea infections (RR=0.78; 95% CI=0.65–0.94).[5] 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.[1] Participants randomised to doxyPEP (n=116) showed a reduction in chlamydia (hazard ratio [HR]=0.30; 95% CI=0.13–0.70) and syphilis (HR=0.27; 95% CI=0.07–0.98), but no statistically different reduction in gonorrhoea (HR=0.83; 95% CI=0.47–1.47). There was no impact on the incidence of *Mycoplasma genitalium*.[6] The DoxyPEP study included 501 participants using HIV PrEP or living with HIV.[3] Participants randomised to doxyPEP (n=339) experienced significant reductions in chlamydia for both HIV PrEP users (RR=0.12; 95% CI=0.05–0.25) and those living with HIV (RR=0.26; 95% CI=0.12–0.57). Similar reductions were observed for syphilis (RR=0.13; 95% CI=0.03–0.59 for HIV PrEP users and RR=0.23; 95% CI=0.04–1.29 for those living with HIV). For gonorrhoea, there was a lesser but statistically significant reduction (RR=0.45; 95% CI=0.32–0.65 for HIV PrEP users and RR=0.43; 95% CI=0.26–0.71 for those living with HIV). A significant reduction in the incidence of STIs per calendar quarter was maintained during the open label extension phase of the trial.[7] The DOXYVAC study included 556 participants using HIV PrEP and also randomised participants to receive the 4CMenB meningococcal vaccination.[2] In keeping with the other studies, doxyPEP significantly reduced chlamydia (adjusted HR [aHR]=0.14; 95% CI=0.09–0.23) and syphilis diagnoses (aHR=0.21; 95% CI=0.11–0.41) but was less effective for gonorrhoea (aHR=0.67; 95% CI=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; 95% CI=0.23–0.46 and IRR=0.22; 95% CI=0.07–0.54, respectively).[8] In the first year of implementation in San Francisco, approximately 20% of GBMSM and TGW attending public sexual health clinics (3,974 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.[9] 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.[10]

Cisgender women: The dPEP Kenya study included 449 cisgender women using HIV PrEP.[4] The results showed no significant effect of doxyPEP (n=224) in reducing STIs compared to standard care (RR=0.88; 95% CI=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.

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.[11]

7. SAFETY

7.1. 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.[1] 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.[3] During the open label extension, there was a single grade 2 lab abnormality (raised alanine aminotransferase) and five grade 3 adverse events (diarrhoea and headache) that were possibly or probably related to doxyPEP.[7] 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.[2] 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.[4]

7.2. 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.[12,13]

7.3. 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.[14] 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.

8. ANTIMICROBIAL RESISTANCE

8.1.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, in line with the National Institute for Health and Care Excellence (NICE) guidelines on long-term prophylactic antibiotic use for other indications (e.g., uncomplicated lower urinary tract infection, bronchiectasis, and acne).[15-17]

Clinical trials evaluating doxyPEP have reported varying levels of tetracycline resistance evolution in *N. gonorrhoeae*, commensal *Neisseria* species, *S. aureus* and the gut microbiome associated with doxyPEP use.[18] In the DoxyPEP study, doxycycline-resistant *N. gonorrhoeae* isolates increased from 27% at baseline to 38% in doxyPEP users, although the number of isolates available for testing was low (15 at baseline, 13 during follow-up).[3] Doxycycline resistance in *S. aureus* isolated from the oro- and nasopharynx increased from 12% at baseline to 16% at 12 months, although overall rates of carriage fell from 45% at baseline to 28% at 12 months.[3] Carriage of commensal *Neisseria* species in the oropharynx was high and remained stable among trial participants throughout follow up, however there was a non-significant increase in the proportion of these isolates with tetracycline resistance among participants in the doxyPEP arm at 12 months compared to baseline (70% vs. 63%, respectively; p=0.11). A significant decrease was seen in the control arm (62% to 42%, p<0.01).[19]

In both the DOXYVAC and dPEP Kenya studies, all *N. gonorrhoeae* isolates were tetracycline resistant at baseline and during follow-up.[2,4] In the DOXYVAC study, rates of detection of methicillin-resistant *S. aureus* (MRSA) and extended-spectrum beta-lactamase producing *Escherichia coli* did not differ between the study arms.

In a study of 2,312 GBMSM diagnosed with gonorrhoea in a sexual health service in Washington, USA, *N. gonorrhoeae* tetracycline resistance increased from 27% in the first calendar quarter of 2023 to 70% in the second calendar quarter (Q2) of 2024, after doxyPEP was introduced in Q2 2023.[20] Taking >3 doses of doxyPEP per month was associated with

tetracycline resistance. This study also found that doxyPEP users had lower rates of *S. aureus* colonisation (27% vs 36%, p=0.02) but *S. aureus* tetracycline resistance was higher (18% vs 8%, p<0.0001). DoxyPEP users also had higher rates of Group A Streptococcus colonisation (9% vs 4%, p=0.008). It has also been suggested that doxyPEP could induce cross-resistance to other antibiotic classes, although these data are from *in silico* studies only.[21,22]

To date, resistance to doxycycline has not been observed in *Treponema pallidum* and *Chlamydia trachomatis*.[23] In a recent in-vitro study, *T. pallidum* did not develop tetracycline-resistance following long-term sub-bactericidal exposure to doxycycline.[18] 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.[1,2,4] 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.[6] 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*).[24-27] Military studies on doxycycline for malaria prophylaxis have reported increased colonisation with multi-drug resistant *E.* coli and tetracycline resistant non-enterotoxigenic *E. coli* (ETEC), but- no significant increase in resistance to doxycycline in *Campylobacter* and ETEC.[28-30] Additionally, AMR emergence in *S. aureus* related to history of daily doxycycline use has been observed.[31,32] 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.

8.2. Microbiome and resistome

The DoxyPEP study included a microbiome and resistome subanalysis (doxyPEP users n=100, control n=50) using self-collected rectal swabs.[33] No difference in bacterial mass, abundance, alpha diversity (bacterial diversity within a sample) or beta diversity (bacterial diversity between samples) was seen between study arms at baseline and 6 months, or within study arms over time. However, higher tetracycline gene expression was seen in doxyPEP users at 6 months, without changes in other antibiotics classes (aminoglycosides, beta-lactams, macrolides/lincosamides/streptogramins). A greater number of doxyPEP doses was associated

with higher levels of tetracycline resistance gene expression. Overall, the resistance gene abundance findings are in keeping with studies from other populations and indications.[34,35]

An RCT of immediate versus deferred daily doxyPEP in GBMSM and TGW (n=52) assessed gut microbiome using rectal swabs.[33] This demonstrated minimal impact on the microbiome with no changes in alpha or beta diversity at the genus and family levels between baseline, week 24, and week 48 ($p>0.05$). However, a decrease in alpha diversity at the order, class, and phylum levels was noted at week 48 in the immediate arm (mean: 0.84 vs. 0.66 at phylum, $p<0.05$), but not in the deferred arm.

Across a range of published microbiome studies, doxycycline exposure has been shown to alter microbial communities in the gut [35-38] and skin.[39,40] However, findings are not consistent, with no changes in skin, gut, or sinonasal bacterial diversity after doxycycline treatment also seen.[41,42]

9. BASELINE ASSESSMENT

9.1. 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.[43]

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 RCTs.

We recommend doxyPEP for cisgender GBMSM and TGW at elevated risk of acquiring syphilis (GRADE 1A). Individuals who may be at increased risk of acquiring syphilis include those with a recent (in the last year) bacterial STI diagnosis or those with 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, 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 a lack of RCT evidence showing the effectiveness of doxyPEP in preventing STI acquisition following receptive vaginal sex. In a small pharmacokinetic study including nine cisgender 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.[44] Whilst available data suggests good protection in cisgender men and TGW 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.

At the time of writing, there is no clinical trial evidence to support a recommendation of doxyPEP for cisgender women and other people assigned female at birth. However, clinicians may consider doxyPEP for people assigned female at birth at elevated risk of acquiring syphilis

(this may include sex workers and transgender men who have sex with men), on a case-by-case basis, and in discussion with the patient (GRADE 2D).

There is a paucity of evidence on the prevalence of STIs post sexual assault, although, in general, the risk of any STI is thought to be low. For this reason, current BASHH guidelines for the management of individuals disclosing sexual violence (2022) do not recommend routine use of antibiotics for prophylaxis against STIs after sexual assault. Clinicians may consider doxyPEP for people at elevated risk of acquiring syphilis attending for clinical care within 72 hours of sexual assault on a case-by-case basis, and in discussion with the patient (GRADE 2D). STI testing and further management of individuals who have experienced sexual violence should be in line with BASHH guidelines. Healthcare providers assessing the need for doxyPEP outside of specialist sexual health services should liaise with local sexual health teams for advice.

9.2. Health equity considerations

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 people who could benefit from doxyPEP. In addition, the current lack of inclusion of key population groups within clinical trials of doxyPEP and lack of RCT evidence of effectiveness in people assigned female at birth perpetuates health inequalities.

9.2.1. Dosage and administration

Recommended dosing regimen:

We recommend taking a single dose of 200 mg (i.e., 2 x 100 mg capsules) 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).

Alternative dosing regimen:

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).

Number of capsules to prescribe:

There is no evidence to guide the optimal number of capsules 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 capsules to cover the period between service contacts, including scheduling of HIV PrEP and regular STI testing. Likewise, the potential impact of prescribing a large excess of capsules should be considered, for example, wastage, incorrect disposal, and sharing of medicines with others.

9.2.2. Pregnancy and Breast/Chest-feeding

Although doxycycline appears to be safe when used in the first trimester of pregnancy, data are limited. In keeping with the recommendation in the BASHH position statement on doxycycline use in pregnancy, we suggest doxyPEP is only used up to 15 weeks' gestation.[45] Outcome and follow up data should be collected to aid future practice. Healthcare professionals can contact UKTIS on 0344 892 0909 to prospectively report doxycycline exposure in pregnancy and UKTIS will ensure follow up.

Although use of doxycycline whilst breastfeeding is contraindicated in the summary of product characteristics (SmPC), very small amounts of doxycycline pass into the breast milk and absorption by the infant is inhibited by the calcium in the breast milk. Short term use of doxycycline is unlikely to cause harm to the breast feeding infant. [46,47]

9.2.3. Baseline screening and diagnostics

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 such as 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.

People living with HIV 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.

9.2.4. 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 around AMR;
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 plenty of fluid 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), safer sex advice and appropriate behaviour change interventions as outlined in UK national guidance;
5. Providing clear information that doxyPEP is only for the prevention of syphilis and chlamydia, that it is not 100% effective at preventing acquisition of these infections, that it is unlikely to prevent gonorrhoea, and does not offer protection against any other STIs. 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 doxycycline at the same time as antacids containing aluminium, calcium, magnesium or oral zinc, iron salts or bismuth preparations. Intake of these substances should be separated from dosing with doxycycline as far as possible and 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. The absorption of doxycycline is not notably influenced by the simultaneous ingestion of milk;

7. Informing users that chronic and heavy alcohol consumption may decrease the effectiveness of doxycycline.

10.MONITORING AND FOLLOW-UP

10.1.1. 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). We recommend that doxyPEP users are encouraged to test for asymptomatic STIs at a frequency recommended in BASHH summary guidance on testing for STIs (GRADE 1D).

The effect on serological response to syphilis infection is not currently known although a small case series suggested possible delayed seroconversion in three men with primary syphilis.[48] 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). However, asymptomatic contacts who consistently use doxyPEP following sex or confirm that they took doxyPEP within 72 hours of the potential exposure, may choose not to receive epidemiological treatment, opting for a 'watch and wait' approach instead. We recommend that all contacts of syphilis should be supported to attend if they develop symptoms of potential syphilis infection and have serological testing at appropriate time points (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). If this test is positive for chlamydia then offer treatment in line with the BASHH guideline on the management of chlamydia (GRADE 1D). We recommend that asymptomatic doxyPEP users who are contacts of gonorrhoea, *M.*

genitalium 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.

10.1.2. 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.

10.2. 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.

11.AUDITABLE OUTCOME MEASURES

- All cisgender GBMSM and TGW at elevated risk of acquiring syphilis are offered doxyPEP (performance standard 97%)
- All people prescribed doxyPEP should be offered information (written or digital) about doxyPEP (performance standard 97%)
- All people prescribed doxyPEP should undergo testing for STIs (performance standard 97%)
- All people prescribed doxyPEP should be offered appropriate vaccines (performance standard 97%)
- All people prescribed doxyPEP should be assessed for eligibility for HIV PrEP (performance standard 97%)

12.RECOMMENDATIONS FOR FUTURE RESEARCH

12.1. 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 (e.g. young people, GBMSM, transgender and non-binary individuals, and racially minoritised groups)?
- 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 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 acquiring syphilis among doxyPEP users, and how do these factors influence recommendations for testing and epidemiological treatment?
- How does doxyPEP use influence sexual behaviour, sexual freedom, sexual pleasure and anxiety 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?
- 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?

12.2. Antimicrobial resistance and monitoring

- 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?
- What is the impact of doxyPEP use on the development of resistance to tetracyclines and other antimicrobials in Gram negative organisms?

13.DISCLOSURES

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13.2. 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.

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13.4. 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.

13.5. 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/.

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14.REFERENCES

1. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis* 2018;18(3):308-17. doi: 10.1016/S1473-3099(17)30725-9 [published Online First: 20171208]
2. Molina JM, Bercot B, Assoumou L, et al. Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2 x 2 factorial design. *Lancet Infect Dis* 2024 doi: 10.1016/S1473-3099(24)00236-6 [published Online First: 20240523]
3. Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *N Engl J Med* 2023;388(14):1296-306. doi: 10.1056/NEJMoa2211934
4. Stewart J, Oware K, Donnell D, et al. Doxycycline prophylaxis to prevent sexually transmitted infections in women. *N Engl J Med* 2023;389(25):2331-40. doi: 10.1056/NEJMoa2304007
5. Sokoll PR, Migliavaca CB, Döring S, et al. Efficacy of postexposure prophylaxis with doxycycline (Doxy-PEP) in reducing sexually transmitted infections: a systematic review and meta-analysis. *Sex Transm Infect* 2025;101(1):59-67. doi: 10.1136/sextrans-2024-056208 [published Online First: 20250129]
6. Bercot B, Charreau I, Rousseau C, et al. High Prevalence and High Rate of Antibiotic Resistance of Mycoplasma genitalium Infections in Men Who Have Sex With Men: A Substudy of the ANRS IPERGAY Pre-exposure Prophylaxis Trial. *Clin Infect Dis* 2021;73(7):e2127-e33. doi: 10.1093/cid/ciaa1832
7. Luetkemeyer AF, Donnell D, Cohen SE, et al. Doxycycline to prevent bacterial sexually transmitted infections in the USA: final results from the DoxyPEP multicentre, open-label, randomised controlled trial and open-label extension. *Lancet Infect Dis* 2025 doi: 10.1016/s1473-3099(25)00085-4 [published Online First: 20250324]
8. Scott H, Roman J, Spinelli MA, et al. Doxycycline PEP: high uptake and significant decline in STIs after clinical implementation. *Conference on Retrovirsuses and Opportunistic Infections (CROI)* 2024
9. Sankaran M, Glidden DV, Kohn RP, et al. Doxy-PEP associated with declines in *Chlamydia* and *Syphilis* in MSM and trans women in San Francisco. *Conference on Retrovirsuses and Opportunistic Infections (CROI)* 2024
10. Traeger MW, Leyden WA, Volk JE, et al. Doxycycline Postexposure Prophylaxis and Bacterial Sexually Transmitted Infections Among Individuals Using HIV Preexposure Prophylaxis. *JAMA Intern Med* 2025 doi: 10.1001/jamainternmed.2024.7186 [published Online First: 20250106]
11. Fredericksen RJ, Perkins R, Brown CE, et al. Doxycycline as Postsexual Exposure Prophylaxis: Use, Acceptability, and Associated Sexual Health Behaviors Among a Multi-Site Sample of Clinical Trial Participants. *AIDS Patient Care STDS* 2024;38(4):155-67. doi: 10.1089/apc.2023.0289
12. Digre KB. Not so benign intracranial hypertension. *Bmj* 2003;326(7390):613-4. doi: 10.1136/bmj.326.7390.613
13. Doxycycline 100 mg capsules - the summary of product characteristics and the patient information leaflet. Sovereign Medical. Last updated 20 June 2024. [Available from: https://www.medicines.org.uk/emc/product/13082/pil#about-medicine.
14. Chan PA, Le Brazidec DL, Becasen JS, et al. Safety of Longer-Term Doxycycline Use: A Systematic Review and Meta-Analysis With Implications for Bacterial Sexually Transmitted Infection Chemoprophylaxis. *Sex Transm Dis* 2023;50(11):701-12. doi: 10.1097/OLQ.0000000000001865 [published Online First: 20230904]
15. National Institute for Health and Care Excellence. Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial prescribing. NICE Guideline [NG117]. NICE; 2018 [cited 2025 April 3]. Available from: https://www.nice.org.uk/guidance/ng117 accessed April 3 2025.
16. National Institute for Health and Care Excellence. Acne vulgaris: management. NICE Guideline [NG198]. London: NICE; 2023 [cited 2025 April 3]. Available from: https://www.nice.org.uk/guidance/ng198 accessed 3 April 2025.
17. National Institute for Health and Care Excellence. Urinary tract infection (recurrent): antimicrobial prescribing. NICE guideline [NG112]. London: NICE; 2024 [cited 2025 April 3]. Available from: https://www.nice.org.uk/guidance/ng112.
18. Tantalo LC, Luetkemeyer A, Lieberman NAP, et al. Long-term in vitro exposure of Treponema pallidum to sub-bactericidal doxycycline did not induce resistance: Implications for doxy-PEP and syphilis. *J Infect Dis* 2024 doi: 10.1093/infdis/jiae381 [published Online First: 20240727]

19. Luetkemeyer A, Donnell D, Dombrowski JC, et al. DoxyPEP and antimicrobial resistance in *N. gonorrhoeae*, commensal Neisseria and *S. aureus*. *CROI 2023, Seattle, Washington* 2023
20. Soge OO, Thibault CS, Cannon CA, et al. Potential Impact of Doxycycline Post-Exposure Prophylaxis on Tetracycline Resistance in Neisseria gonorrhoeae and Colonization with Tetracycline-Resistant Staphylococcus aureus and Group A Streptococcus. *Clin Infect Dis* 2025 doi: 10.1093/cid/ciaf089 [published Online First: 20250228]
21. Vanbaelen T, Manoharan-Basil SS, Kenyon C. Doxycycline Postexposure Prophylaxis Could Induce Cross-Resistance to Other Classes of Antimicrobials in Neisseria gonorrhoeae : An In Silico Analysis. *Sex Transm Dis* 2023;50(8):490-93. doi: 10.1097/OLQ.0000000000001810 [published Online First: 20230323]
22. Gestels Z, Manoharan-Basil SS, Kenyon C. Doxycycline post exposure prophylaxis could select for cross-resistance to other antimicrobials in various pathogens: An in silico analysis. *Int J STD AIDS* 2023;34(13):962-68. doi: 10.1177/09564624231190108 [published Online First: 20230719]
23. Jensen JS, Unemo M. Antimicrobial treatment and resistance in sexually transmitted bacterial infections. *Nat Rev Microbiol* 2024;22(7):435-50. doi: 10.1038/s41579-024-01023-3 [published Online First: 20240320]
24. Legiawati L, Halim PA, Fitriani M, et al. Microbiomes in Acne Vulgaris and Their Susceptibility to Antibiotics in Indonesia: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)* 2023;12(1) doi: 10.3390/antibiotics12010145 [published Online First: 20230111]
25. Nakase K, Koizumi J, Fukumoto S, et al. Increased Prevalence of Minocycline-Resistant Staphylococcus epidermidis with tet(M) by Tetracycline Use for Acne Treatment. *Microb Drug Resist* 2022;28(8):861-66. doi: 10.1089/mdr.2021.0319 [published Online First: 20220620]
26. Moon SH, Roh HS, Kim YH, et al. Antibiotic resistance of microbial strains isolated from Korean acne patients. *J Dermatol* 2012;39(10):833-7. doi: 10.1111/j.1346-8138.2012.01626.x [published Online First: 20120711]
27. Tan HH, Goh CL, Yeo MG, et al. Antibiotic sensitivity of Propionibacterium acnes isolates from patients with acne vulgaris in a tertiary dermatological referral centre in Singapore. *Ann Acad Med Singap* 2001;30(1):22-5.
28. Buchek G, Mende K, Telu K, et al. Travel-associated multidrug-resistant organism acquisition and risk factors among US military personnel. *J Travel Med* 2021;28(3) doi: 10.1093/jtm/taab028
29. Arthur JD, Echeverria P, Shanks GD, et al. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria prophylaxis. *Am J Trop Med Hyg* 1990;43(6):608-13. doi: 10.4269/ajtmh.1990.43.608
30. Vento TJ, Cole DW, Mende K, et al. Multidrug-resistant gram-negative bacteria colonization of healthy US military personnel in the US and Afghanistan. *BMC Infect Dis* 2013;13:68. doi: 10.1186/1471-2334-13-68 [published Online First: 20130205]
31. Lesens O, Haus-Cheymol R, Dubrous P, et al. Methicillin-susceptible, doxycycline-resistant Staphylococcus aureus, Cote d'Ivoire. *Emerg Infect Dis* 2007;13(3):488-90. doi: 10.3201/eid1303.060729
32. Mende K, Beckius ML, Zera WC, et al. Lack of doxycycline antimalarial prophylaxis impact on Staphylococcus aureus tetracycline resistance. *Diagn Microbiol Infect Dis* 2016;86(2):211-20. doi: 10.1016/j.diagmicrobio.2016.07.014 [published Online First: 20160715]
33. Burgener AD, Grennan T, Knodel S, et al. DoxyPEP impact on the microbiome of men who have sex with men and transgender women on HIV PrEP. *CROI 2025, San Francisco, California* 2025
34. Carpenter L, Miller S, Flynn E, et al. Exposure to doxycycline increases risk of carrying a broad range of enteric antimicrobial resistance determinants in an elderly cohort. *Journal of Infection* 2024;89(4) doi: 10.1016/j.jinf.2024.106243
35. Kang K, Imamovic L, Misiakou MA, et al. Expansion and persistence of antibiotic-specific resistance genes following antibiotic treatment. *Gut Microbes* 2021;13(1):1-19. doi: 10.1080/19490976.2021.1900995
36. Cheung MK, Ng RWY, Lai CKC, et al. Alterations in faecal microbiome and resistome in Chinese international travellers: a metagenomic analysis. *Journal of Travel Medicine* 2023;30(6) doi: 10.1093/jtm/taad027
37. Javelle E, Mayet A, Million M, et al. Gut Microbiota in Military International Travelers with Doxycycline Malaria Prophylaxis: Towards the Risk of a Simpson Paradox in the Human Microbiome Field. *Pathogens* 2021;10(8) doi: 10.3390/pathogens10081063 [published Online First: 20210821]
38. Mättö J, Maukonen J, Alakomi HL, et al. Influence of oral doxycycline therapy on the diversity and antibiotic susceptibility of human intestinal bifidobacterial population. *J Appl Microbiol* 2008;105(1):279-89. doi: 10.1111/j.1365-2672.2008.03792.x [published Online First: 20080404]
39. Jo J-H, Harkins CP, Schwardt NH, et al. Alterations of human skin microbiome and expansion of antimicrobial resistance after systemic antibiotics. *Science Translational Medicine* 2021;13(625):eabd8077. doi: doi:10.1126/scitranslmed.abd8077

40. Park S-Y, Kim HS, Lee SH, et al. Characterization and Analysis of the Skin Microbiota in Acne: Impact of Systemic Antibiotics. *Journal of Clinical Medicine* 2020;9(1):168.
41. Siu J, Mackenzie BW, Klingler L, et al. Sinonasal and gastrointestinal bacterial composition and abundance are stable after 1 week of once-daily oral antibiotic treatment for chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2021;11(9):1355-66. doi: 10.1002/alr.22799 [published Online First: 20210420]
42. Woo YR, Lee SH, Cho SH, et al. Characterization and Analysis of the Skin Microbiota in Rosacea: Impact of Systemic Antibiotics. *Journal of Clinical Medicine* 2020;9(1):185.
43. Sun S, Narayanan P, Vickers A, et al. GRASP report: data to August 2024. London: UK Health Security Agency, 2024.
44. Haaland RE, Fountain J, Edwards TE, et al. Pharmacokinetics of single dose doxycycline in the rectum, vagina, and urethra: implications for prevention of bacterial sexually transmitted infections. *EBioMedicine* 2024;101:105037. doi: 10.1016/j.ebiom.2024.105037 [published Online First: 20240229]
45. Grant A. BASHH position statement on doxycycline use in pregnancy. 2024
46. Electronic Medicines Compendium. Doxycycline 100mg Capsules - Summary of Product Characteristics (SmPC) UK: Datapharm; 2021 [cited 2025 April 3]. Available from: https://www.medicines.org.uk/emc/product/13082/smpc accessed April 3 2025.
47. Drugs and Lactation Database (LactMed). Doxycycline https://www.ncbi.nlm.nih.gov/books/NBK500561/#:~:text=A%20number%20of%20reviews%20have,(thrush%2C%20diaper%20rash)2024 [
48. Raccagni AR, Bruzzesi E, Castagna A, et al. Doxycycline postexposure prophylaxis may delay seroconversion in incident syphilis. *Sexually Transmitted Infections* 2024;100(6):397. doi: 10.1136/sextrans-2024-056240

15.APPENDICES

15.1. 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].

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.

[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

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.

15.2. 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 [2,3,4,5,6,7].

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:

[2] Guyatt GH, Oxman AD, Vist G, et al; GRADE Working Group. BMJ 2008; 336:924-926.

[3] Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7651):995-8.

[4] Schünemann HJ, Oxman AD, Brozek J, et al; GRADE Working Group. BMJ 2008; 336(7653):1106-10.

[5] Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7654):1170-3.

[6] Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. BMJ 2008; 336(7652):1049-51.

[7] Jaeschke R, Guyatt GH, Dellinger P, et al; GRADE working group. BMJ 2008; 337:a744.

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

2. 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.

3. 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?

4. 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.

5. Using the GRADE grid to resolve differences:

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

6. 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.

15.3. Search Strategies

Efficacy of doxycycline as PEP to prevent bacterial STIs:

- Search period for articles: 01-JAN-2018 to 03-APR-2025.
- 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 03-APR-2025.
- 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 03-APR-2025.
- 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.

15.4. Equality Impact Assessment Table version 0.2 dated 8th April 2025

BASHH Guideline Equality Impact Assessment *(based on NICE documentation shared with BASHH August 2019)*				
Guidance title: UK National Guideline for the Use of Doxycycline Post Exposure Prophylaxis (DoxyPEP) for the Prevention of Bacterial Sexually Transmitted Infections (STIs)		**Completed by: JOHN SAUNDERS**		**Date: 08 April 2025**
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	The intervention described (doxyPEP) has been shown in 3 RCTs to significantly reduce the incidence of chlamydia and syphilis among cisgender GBMSM and TGW users with a variable impact on gonorrhoea. A single RCT in cisgender women did not show any impact on the incidence of bacterial STIs although this is likely explained by sub-optimal adherence to the	The guideline highlights the lack of effectiveness data to support a recommendation for use in cisgender women, transgender men and other people assigned female at birth. We highlight that this is a potential source of inequality. Clinicians may consider prescribing doxyPEP for people assigned female at birth on a case by case basis.	Addressing rising rates of STIs is a priority for local government, services and public health agencies in the UK. This guideline offers a new biomedical prevention tool to prevent syphilis (and chlamydia although this is not the major focus of the intervention currently).	Only able to recommend doxyPEP for GBMSM and TGW. Clinicians may consider prescribing for people assigned female at birth on a case by case basis.

	intervention. However, the guideline will only recommend doxyPEP for cisgender GBMSM and TGW. Whilst this group are disproportionately affected by syphilis diagnoses in the UK, the greatest burden and harms associated with chlamydia is in cisgender women and other people with a womb and ovaries. For people assigned female at birth who are at risk of syphilis, clinicians may consider prescribing doxyPEP on a case by case basis.			
Race	Rates of STIs, including syphilis and chlamydia, are not equal across ethnicities. Particularly, those from black ethnicities are disproportionately affected.	doxyPEP use not restricted by this protected characteristic. However, opportunities to identify doxyPEP candidates and prescribe doxyPEP will be influenced by service access which is not equal across different ethnicities according to need.	N/A	N/A
Disability	Surveillance data does not tell us about any association between syphilis and chlamydia and disability. Some people with physical and learning disabilities may be vulnerable to acquiring STIs. Departmental safeguarding procedures	The guidelines are primarily for those working in level 3 specialist sexual health services and safeguarding concerns should be addressed by departmental policies. GU physicians receive level 3 safeguarding training. Services should	Safeguarding concerns should be addressed.	Consideration of patients in these groups being at risk of sexual exploitation/abuse should be made as part of GUM departments safeguarding training.

	should be in place to identify and respond to any issues.	ensure that barriers to accessing services do not disproportionately affect those with disabilities.		
Age	Some young people may be vulnerable to experiencing sexual coercion and violence. Departmental safeguarding procedures should be in place to identify and respond to any issues.	The guidelines are primarily for those working in level 3 specialist sexual health services and safeguarding concerns should be addressed by departmental policies. GU physicians receive level 3 safeguarding training.	Safeguarding concerns should be addressed.	Consideration of patients in these groups being at risk of sexual exploitation/abuse should be made as part of GUM departments safeguarding training.
Sexual orientation	The majority of syphilis diagnoses in the UK are among GBMSM (although gonorrhoea is the most commonly diagnosed bacterial STI in this group). RCT evidence supports the use of doxyPEP for GBMSM to reduce the incidence of syphilis.	N/A	N/A	N/A
Gender reassignment	There is limited data about syphilis in people following gender reassignment. RCT evidence supports the use of doxyPEP for transgender women to reduce the incidence of syphilis.	The guideline provides recommendations for doxyPEP in transgender women. There is insufficient evidence to know if doxyPEP is effective in people with a womb and ovaries including transgender men and other	N/A	N/A

		people assigned female at birth. We have removed, as far as possible, gendered language where this is not relevant to the information provided.		
Religion/belief	Surveillance data does not tell us about any association between STIs and religion/ belief. This is not addressed in the guideline.	N/A	N/A	N/A
Pregnancy & maternity	There is currently insufficient evidence to recommend doxyPEP for people who can become pregnant. Vertical transmission of syphilis is a major adverse health outcome and we acknowledge this in the guideline. We make a recommendation that doxyPEP should be considered for men who have concurrent male and female partners as a way to try and mitigate the risk of syphilis transmission to their female partner(s). Whether this will have a significant impact on neonatal syphilis is not known (and probably unlikely given the low numbers of cases currently seen in the UK context).	N/A	N/A	We do not offer and y specific guidance for doxyPEP management in people who can become pregnancy/ during pregnancy and/or for those who are breast or chest feeding. This is because there is insufficient evidence to show that doxyPEP is effective at preventing STIs in cisgender women, therefore doxyPEP is not recommended for this group.

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	Rates of syphilis and chlamydia are greatest among people residing in areas of greater deprivation. There are geographical variation in access to testing and treatment for STIs, including syphilis and chlamydia. Surveillance data does not offer sufficient granularity to comment on how other inclusion populations may be more affected by these infections. Some people in this inclusion health populations may be vulnerable to additional adverse determinants of health including sexual coercion and violence. Departmental safeguarding procedures should be in place to identify and respond to any issues.	The guidelines are primarily for those working in level 3 specialist sexual health services and safeguarding concerns should be addressed by departmental policies. GU physicians receive level 3 safeguarding training.	Safeguarding concerns should be addressed.	Consideration of patients in these groups being at risk of sexual exploitation/abuse should be made as part of GUM departments safeguarding training.