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GUIDANCE

Public health considerations on the use of doxycycline for post-exposure prophylaxis for bacterial sexually transmitted infections in the EU/EEA

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This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Otilia Mårdh.

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Abbreviations

AMR	Antimicrobial resistance
CDC	United States Centers for Disease Prevention and Control
Doxy-PEP	Doxycycline post-exposure prophylaxis
Doxy-PrEP	Doxycycline pre-exposure prophylaxis
EMIS-2024	The European Men Who Have Sex with Men and Trans People Internet Survey 2024
EU/EEA	European Union/European Economic Area
HIV-PrEP	HIV pre-exposure prophylaxis
IUSTI	International Union against Sexually Transmitted Infections
RCT	Randomised clinical trials
STI	Sexually transmitted infections
WHO	World Health Organization

Key considerations

For more than a decade, bacterial sexually transmitted infections (STIs) have been increasing across the EU/EEA. Men who have sex with men, particularly those living with HIV or using HIV pre-exposure prophylaxis, are overrepresented in case notifications for bacterial STIs such as gonorrhoea, syphilis, lymphogranuloma venereum, and, more recently, chlamydia. There is therefore a need to strengthen existing prevention strategies and explore new approaches.

In clinical trials, doxycycline post-exposure prophylaxis (doxy-PEP) - defined as taking a single 200 mg dose of doxycycline within the first 24 hours and no longer that 72 hours after condomless sex - has shown to be effective in reducing chlamydia and syphilis incidence among men who have sex with men and transgender women. It has also shown to be effective in real-world settings when integrated into comprehensive sexual health strategies for individuals at high risk of acquiring an STI.

However, research also indicates that doxy-PEP may contribute to the development of antimicrobial resistance in targeted bacterial pathogens and bystander organisms, not only among doxy-PEP users, but also among non-users, such as those within sexual networks, the wider community of men who have sex with men, and potentially, the broader population.

Across the EU/EEA, existing guidelines on doxy-PEP vary. Some authorities recommend its use on a case-by-case basis, primarily for syphilis prevention among men who have sex with men and transgender women at high risk of acquiring an STI, while others advise against it. These differing positions reflect ongoing uncertainty regarding the public health benefits of this prophylactic intervention balanced with its potential harms, particularly the risk of increasing antimicrobial resistance.

Regardless of national recommendations, doxy-PEP use is expanding among men who have sex with men in the EU/EEA, both through off-label medical prescription and self-sourcing.

The purpose of this document is to support public health actions in countries or regions that are considering doxy-PEP as a component of comprehensive and integrated sexual health and bacterial STI prevention strategies among men who have sex with men and transgender women at high risk of acquiring syphilis.

The document summaries key findings on:

- the efficacy of doxy-PEP in reducing incident bacterial STI in clinical trial settings among men who have sex with men and transgender women at high risk of acquiring a bacterial STI;
- the impact of doxy-PEP on bacterial STI incidence among men who have sex with men and transgender women in real-world settings, where doxy-PEP clinical guidelines are implemented;
- the potential impact of doxy-PEP on antimicrobial resistance in sexually and non-sexually transmitted pathogens at user and community levels;
- the extent of doxy-PEP use and the characteristics of people using it in EU/EEA countries

ECDC recommends that decisions regarding the use of doxy-PEP should be made at the individual level and follow clinical judgement and national guidelines. ECDC does not recommend a population-level intervention at this time.

The document outlines key considerations from a public health perspective to support public health practice related to this:

- Where implemented, doxy-PEP should be positioned as part of a comprehensive and medically guided sexual health approach that includes access to sexual health services, regular testing and monitoring, periodic reassessment of individual needs, and awareness raising on antimicrobial resistance.
- Doxy-PEP should be focused on syphilis prevention and targeted to groups at highest risk, based on epidemiological evidence, while addressing the needs of specific populations and considering both individual and event-driven risk profiles.
- It is essential that national public health authorities maintain oversight of doxy-PEP use and its impact on STI incidence, antimicrobial resistance and antimicrobial consumption through robust surveillance systems. These should include genomic surveillance, predefined resistance thresholds to guide implementation decisions, and strengthened laboratory capacity for diagnosis, susceptibility testing, and molecular typing of *Chlamydia trachomatis*, *Neisseria gonorrhoea,* and *Treponema pallidum.*
- National public health authorities are encouraged to work in partnership with key stakeholders, including clinical bodies and community organisations, and to consider a set of core principles for effective oversight and evaluation.

Introduction

For more than a decade, the European Union and European Economic Area (EU/EEA) has seen a rise in bacterial sexually transmitted infections (STIs), especially among men who have sex with men and, more recently, among young heterosexual people [1-3]. If left untreated, *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Treponema pallidum* infections can lead to sexual and reproductive health complications [4-6]. In clinical trial settings in France [7,8] and the United States [9], a single 200 mg dose of doxycycline, taken within 72 hours after condomless sex, has proven effective in preventing chlamydia and syphilis among men who have sex with men and transgender women with a history of STIs. In response to these findings, several national bodies and professional organisations (from Australia, the United States and Europe) have issued guidelines recommending post-exposure prophylaxis with 200 mg doxycycline (doxy-PEP) within the first 24 hours, and no longer that 72 hours, after condomless sex for individuals at high risk of acquiring a bacterial STI, most frequently defined as bacterial STI diagnosis in the past 12 months [10-14]. These guidelines also note uncertainties on the overall public health impact and the potential for increased antimicrobial resistance.

This report is a result of a meeting of the European STI Network in Stockholm, in June 2023, where national experts requested ECDC provide public health considerations on the use of doxycycline for STI prophylaxis for the EU/EEA [15], to support decision-making in the Region.

Current STI epidemiology trends in the EU/EEA

Sexually transmitted infections are a global public health concern due to their high prevalence, potential for serious complications on sexual and reproductive health when left untreated, and increasing antimicrobial resistance to current treatments [16]. There is a pressing need for novel preventive interventions.

Over the past decade, bacterial STIs have continued to rise in the EU/EEA, driven by a range of factors [17]. While part of this increase may be attributed to expanded testing in certain populations, it also reflects persistent vulnerabilities and highlights a continuous need to strengthen and tailor prevention efforts. In 2023, bacterial STI notifications in the EU/EEA reached a record high of over 370 000 cases, with overall notification rates increased by 16% for chlamydia, 138% for gonorrhoea, and 53% for syphilis since 2019 [1-3]. Men who have sex with men were disproportionately represented, accounting for 73% of syphilis, 58% of gonorrhoea, and 20% of chlamydia cases in 2023. Men who have sex with men and are living with HIV are overrepresented in bacterial STI notifications. A steep increase has also been observed in recent years among men who have sex with men with HIV-negative status. This increase is likely an effect of enhanced screening, particularly among men who have sex with men using HIV pre-exposure prophylaxis (HIV-PrEP). Consistent with surveillance data, prevalence estimates from a recent systematic review indicate high levels of chlamydia, gonorrhoea, and syphilis among men who have sex with men, particular among those attending STI clinics, living with HIV, or using HIV-PrEP [18].

Over the past decade, gonorrhoea and syphilis notifications have fluctuated at considerably lower levels among heterosexual populations in the EU/EEA. However, an upsurge in gonorrhoea notifications has been observed in 2022 and 2023, particularly among individuals aged 20–24 years. Public health responses in countries observing increases include interventions to raise awareness among young people about the risks of STIs, the importance of safe sexual practices and quickly seeking testing following a possible exposure [19].

In an ECDC study on the burden of communicable diseases in the EU/EEA for 2009–2013, chlamydia, gonorrhoea and syphilis were associated with comparatively low disability-adjusted life years per 100 000 population and per case among the 31 diseases assessed [20]. Up-to-date evidence is needed to contextualise and quantify the impact of recent upsurges in bacterial STI notifications on the burden of disease and the financial costs and to inform future policy decision-making.

In the EU/EEA, men who have sex with men attending STI clinics, using HIV-PrEP, or living with HIV, are disproportionally affected by bacterial STIs

In the EU/EEA, more than half of newly-diagnosed *Neisseria gonorrhoeae and Treponema pallidum* infections are reported among men who have sex with men, with sharp increases observed in recent years. *Chlamydia trachomatis* notifications among men who have sex with men are also rising, largely due to frequent screening of HIV-PrEP users. The highest prevalence of these infections is observed among men who have sex with men attending STI clinics, using HIV-PrEP, or living with HIV.

Doxycycline post-exposure prophylaxis

Doxycycline post-exposure prophylaxis (doxy-PEP) is a biomedical intervention that refers to taking a single 200 mg dose of doxycycline within 24 hours and no later than 72 hours after a possible sexual exposure such as condomless sex (oral, anal or vaginal). In clinical trial settings, it has proven effective in reducing incident *Chlamydia trachomatis* and *Treponema pallidum* (syphilis) among men who have sex with men and transgender women at risk for STIs. For EU/EEA settings, a reduction in incident *Neisseria gonorrhoeae* infections is unlikely due to existing high prevalence of resistance to tetracyclines. A summary of reported efficacy from clinical trials is presented in the 'Results and key findings' section of this document. Details on how doxy-PEP should be integrated as a component in a comprehensive sexual health strategy rather than as a stand-alone intervention can be found in the 'Considerations from a public health perspective' section.

What is doxy-PEP?

Doxycycline post-exposure prophylaxis (doxy-PEP) is defined as taking 200 mg of doxycycline within 24 hours and no later than 72 hours after condomless sex (oral, anal or vaginal), to reduce incident chlamydia and syphilis infections, in particular among men who have sex with men and transgender women at risk for STIs.

Note: Doxycycline is a prescription-only, broad-spectrum antibiotic used in Europe to treat a wide range of bacterial infections. It is commonly prescribed for respiratory and urinary tract infections, acne, and sexually transmitted infections such as chlamydia, lymphogranuloma venereum (LGV), and syphilis [21,22]. It is also used to treat less common infections, including tick-borne diseases (e.g. Lyme disease, anaplasmosis, ehrlichiosis), plague, brucellosis, cholera, and anthrax. Additionally, doxycycline is approved for malaria prophylaxis in travellers to regions with chloroquine-resistant Plasmodium falciparum. The 2025 IUSTI Europe guidelines now recommend doxycycline as first-line therapy for chlamydia, replacing single-dose azithromycin due to increasing resistance to azithromycin in M. genitalium, a frequent co-infection [6]. Doxycycline is contraindicated in individuals with hypersensitivity to tetracyclines, in those with obstructive oesophageal disorders, during pregnancy and breastfeeding, and in children under eight years of age.

Guidelines, recommendations and statements on doxy-PEP

Following the publication of clinical trials results, several countries, including the United States [10], Canada [23,24] and Australia [11], have issued guidelines on doxy-PEP indicating priority groups and details on follow-up. The European AIDS Clinical Society included doxy-PEP in its 2023 guidelines under the section on bacterial STI prophylaxis [12]. In 2024, the International Union against Sexually Transmitted Infections (IUSTI) Europe released a position statement highlighting substantial uncertainties regarding the long-term benefits, population-level impact, emergence of antimicrobial resistance, and the scalability of doxy-PEP within health systems [13]. In 2025, the British Association for Sexual Health and HIV published national evidence-based guidelines recommending doxy-PEP as part of a comprehensive STI prevention strategy, in response to rising rates of syphilis [25]. Within the EU/EEA, guidance or position statements from national clinical organisations have been released in Austria (2024) [26], Belgium (2023) [27], Czechia (2024) [28], France (2025) [29], Germany (2023) [14], Ireland (2024) [30], the Netherlands (2025) [31], Poland (2025)[32] and Spain (2024)[33]. Most of these guidelines advise against the use of doxy-PEP at the population level, instead recommending a case-by-case approach, particularly for individuals at high risk of acquiring STIs, as a part of a comprehensive approach to sexual health. A summary of the above-mentioned guidelines is provided in Annex 3.

Scope and intended audience

The purpose of this document is to support public health practice in EU/EEA countries that are considering doxy-PEP as a component of comprehensive and integrated sexual health and bacterial STI prevention strategies, with a focus on men who have sex with men and transgender women.

To achieve this goal, the document summarises the current evidence on:

- the efficacy of doxy-PEP in reducing incident bacterial STIs in clinical trial settings among men who have sex with men and transgender women at high risk of acquiring a bacterial STI;
- the impact of doxy-PEP on bacterial STIs incidence among men who have sex with men and transgender women in real-world settings where doxy-PEP clinical guidelines are implemented;
- the potential impact of doxy-PEP on antimicrobial resistance in sexually and non-sexually transmitted pathogens at user and community levels;
- the extent of doxy-PEP use and the characteristics of people who use it in EU/EEA countries.

Additional topics addressed/covered to a lesser extent include the impact on antimicrobial consumption and potential implications for syphilis diagnostics.

The document also looks at key considerations regarding the use of doxy-PEP to support public health practice.

The intended audience includes public health professionals and national authorities in the EU/EEA involved in STI prevention and control, STI monitoring and AMR surveillance. This document also addresses healthcare providers and civil society organisations in Europe who play a key role in advancing effective, community-informed sexual health programmes.

Guidance development

The public health considerations outlined in this document are informed by a rapid literature review, complemented by a desk review, European surveys, and input from an Expert Advisory Group convened by ECDC.

An Expert Advisory Group was convened by ECDC in October 2024 (see section below for further details on group composition) to assist ECDC in identifying priority questions that would guide public health considerations for doxy-PEP implementation in the EU/EEA.

Based on these research questions, evidence was derived from several sources (Table 1). A rapid literature review was carried out by Statens Serum Institut (SSI), Denmark (see further details below). Additional studies published after the period of the rapid literature review and identified by ECDC or the Advisory Group were included through a desk review (see further details below).

Two European surveys provided further data: i) the European Men Who Have Sex with Men and Trans People Internet Survey (EMIS)-2024 [34] and ii) the ECDC 2024 survey on monitoring of the responses to sexually transmitted infection epidemics in EU/EEA countries [35] (see further details on both studies below).

Table 1 summarises the research questions and corresponding evidence sources.

Table 1. Research questions and evidence used

Research question	Evidence used
What is the efficacy of doxy-PEP to prevent incident bacterial STIs?	Rapid literature review Desk review
What is the impact of doxy-PEP on bacterial STI incidence outside of clinical trial settings?	Rapid literature review Desk review
What is the impact of doxy-PEP on antimicrobial resistance in sexually and non-sexually transmitted pathogens?	Rapid literature review Desk review
What is the extent of doxy-PEP use and what are characteristics of users in the EU/EEA?	EMIS-2024 survey, ECDC 2024 STI Monitoring survey Desk review

Evidence addressing the four questions is presented in a narrative manner and was not assessed using a grading methodology due to heterogeneity, the evolving nature of the evidence during the course of the project, and because the main aim of the document was not to recommend doxy-PEP as an intervention, but to support national STIs prevention programmes, including those considering the implementation of doxy-PEP recommendations.

Findings were presented to and discussed with the Expert Advisory Group, which provided input on interpretation and considerations for implementation within the EU/EEA context.

Expert Advisory Group consultation

In 2024, ECDC established an Expert Advisory Group on 'Doxycycline prophylaxis of bacterial STIs in the EU/EEA - considerations for public health practice', combining independent expertise and stakeholder representation. The Group comprised experts from a broad range of competency areas that included: civil society engagement, public health epidemiology and microbiology within the STI Network, antimicrobial resistance of bacterial STIs, antimicrobial resistance with a broader scope, clinical trials on doxy-PEP, sexual healthcare/clinicians, human microbiome research, and STI-related policy making (Annex 1).

Representatives of regulatory bodies (European Medicine Agency) and other organisations (WHO Regional Office for Europe, IUSTI Europe, the US CDC) were also included in the Group. Experts were identified through nominations received from the ECDC STI Network, via the ECDC Expert Directory [36], or through nominations by aforementioned organisations. Declarations of interest were reviewed for all Advisory Group members. Participation in the group was not subject to financial remuneration.

According to its terms of reference, the group had a consultative role; the overall responsibility for formulating public health considerations on doxy-PEP in the EU/EEA remained with ECDC.

The Expert Advisory Group advised ECDC on priority questions and remaining knowledge gaps, contributed contextual and technical insights, including new and emerging studies, and informed and reviewed the resulting public health considerations.

Four meetings of this group were organised by ECDC (virtual meetings in October 2024, January 2025, March 2025 and an in-person meeting in June 2025, in Stockholm, at ECDC). During the initial meeting in October 2024, the group assisted ECDC to identify priority topics of public health relevance related to doxy-PEP by ranking a list of questions proposed by ECDC. The highest-ranked topics, formulated as research questions were:

- Which populations are most likely to benefit from doxy-PEP in the EU/EEA?
- What is the potential impact of doxy-PEP on antimicrobial resistance?
- What is the likely impact of doxy-PEP on the incidence of bacterial sexually transmitted infections?
- What are the key health promotion and risk communication messages in relation to doxy-PEP for different groups, including users, healthcare providers, policy makers?

Annex 2 provides details on the scoring and ranking of topics with public health relevance by the group in October 2024. A (non-edited version) full report is available by request.

Furthermore, at the October 2024 meeting, three key areas were outlined for monitoring the impact of doxy-PEP: i) the impact on antimicrobial resistance and consumption; ii) trends in STI incidence, and iii) user characteristics and needs. These areas are highlighted in the chapter 'Considerations from a public health perspective' in this document.

In two follow-up meetings (January and March 2025), the group discussed and assessed the evidence gathered through the rapid review, as well as data on doxy-PEP from EMIS-2024 and the 2024 ECDC STI Monitoring survey. These discussions provided input on considerations for implementation of doxy-PEP in the EU/EEA from a public health perspective, which were formulated into a first draft of this document by ECDC.

The draft summary of evidence from the literature review, together with draft key public health considerations were shared with the group for review, and subsequently discussed, at a one-day in-person meeting on 10 June 2025. Final considerations were developed based on consensus opinion and, where consensus was not clear, voting was used to decide.

During all meetings of the expert group, new or emerging studies identified by the group were included in the document, where relevant to the research questions and/or considerations for public health.

The group advised that the present document should provide an overview of public health considerations regarding doxy-PEP implementation, but should avoid providing, or being perceived as providing, recommendations on EU/EEA-wide implementation. It was also suggested that existing uncertainties be emphasised, particularly the insufficient data on long-term safety, population level effects and the potential impact on antimicrobial resistance. Experts unanimously underlined the importance of community involvement in the oversight of doxy-PEP use and impact.

Rapid literature review

The review followed the Cochrane Guidance for Rapid Review [37]. The objectives for the review were broad: 1) to identify studies exploring the impact of doxy-PEP on the incidence of bacterial STIs among men who have sex with men and transgender women and 2) to determine factors influencing the impact of doxy-PEP as a public health intervention and key elements for policymaking.

The search strategy applied a mix of general and database specific keywords in the title, abstract, or text of the source, including a date filter. The search strategy was subjected to internal critical scientific evaluation using the Peer Review of Electronic Strategies (PRESS) elements [38]. The search strategy is available upon request.

Studies were included if the population consisted of men who have sex with men and transgender women, and if doxy-PEP was evaluated as the intervention. No comparator was required. Eligible studies reported on at least one of the following outcomes: changes in the incidence of chlamydia, gonorrhoea or syphilis; factors influencing the impact of doxy-PEP as an intervention; or key elements relevant to policy decisions on doxy-PEP implementation. Studies were excluded if they were individual case reports or examined doxy-PEP for the prevention of infections other than syphilis, gonorrhoea, or chlamydia.

Literature searches were conducted in PubMed, Embase, The Cochrane Library, and grey literature for studies published between 18 October 2024 and 1 January 2015, with no geographical or language restrictions applied. A total of 407 records were screened, with 153 articles undergoing full-text review, and 59 articles included in the final synthesis. The risk of bias was assessed using a modified version of the JBI critical appraisal tool for analytical cross-sectional studies [39], and study results were synthesised and categorised in accordance with the review objectives.

Desk review

A desk review of the period January 2025 to October 2025 was conducted to supplement the initial literature search. This included targeted searches of grey literature, official websites of clinical organisations, and national public health authorities across Europe. Additional studies published after the rapid literature review were identified and included, based on input from ECDC and the Advisory Group.

European surveys

Data on the prevalence of antibiotic prophylaxis use for STI prevention among men who have sex with men in Europe, which may include the use of doxy-PEP, and sources of antibiotics acquisition were extracted from the European Men Who Have Sex with Men and Trans People Internet Survey (EMIS-2024).

Data on the existence of national policies or clinical guidelines on doxy-PEP, alongside information on informal use, were obtained via the 2024 ECDC survey of the STI Network on monitoring of the responses to sexually transmitted infection epidemics in EU/EEA countries, and updated via desk review, and following suggestions from the group.

Key findings from a public health perspective

This chapter summarises key findings from a public health perspective on the following topics:

- Efficacy in reducing incident bacterial STIs;
- Impact on bacterial STI incidence outside of clinical trial settings;
- Impact on antimicrobial resistance;
- Current use and the characteristic of people who use it.

Efficacy of doxy-PEP in reducing incident bacterial STIs in clinical trials

High-quality evidence from three open-label randomised controlled trials demonstrates that a 200 mg dose of doxy-PEP taken within 24 hours, and no later than 72 hours after condomless sex, significantly reduces the incidence of chlamydia and syphilis among men who have sex with men and transgender women living with HIV and/or using HIV-PrEP, with a history of STIs in the past year [7-9]. In the IPERGAY sub-study in France, doxy-PEP led to a 70% reduction in chlamydia and 73% reduction in syphilis, with no effect on gonorrhoea, after nine months of follow-up. In the United States-based DoxyPEP study, men who have sex with men and transgender women living with HIV had reductions of 74% in chlamydia, 77% in syphilis, and 57% in gonorrhoea, while those on HIV-PrEP showed even greater reductions of 88% for chlamydia, 87% for syphilis, and 55% for gonorrhoea at 12 months of follow-up. Similarly, the DOXYVAC trial in France, among men who have sex with men on HIV-PrEP with high rates of prior STIs, reported reductions of 86% in chlamydia, 79% in syphilis, and 33% in gonorrhoea.

During the 12-month open-label follow-up of the US study, reductions in STIs remained among those continuing doxy-PEP, despite a doubling of sexual partners and condomless anal sex [40]. In the open-label follow-up extension, doxy-PEP was well tolerated, highly acceptable to participants, and no new safety signals were identified [40].

A trial conducted among cisgender women aged 18–30 years in Kenya found that doxy-PEP was not effective in reducing the incidence of chlamydia or gonorrhoea compared with standard care (relative risk (RR)=0.88; 0.60–1.29); however, adherence was low, and the trial was not able to assess effectiveness against syphilis [41]. Nonetheless, the high concentrations of doxycycline found in vaginal tissues among women in a pharmacokinetic study suggest that doxycycline prophylaxis could also be effective in women, and warrants further research on its efficacy in this population [42].

Other effects reported by many doxy-PEP users include a decrease in anxiety and stigma. Some users also describe an empowering effect that facilitates sex positivity and allows individuals to take control of their own sexuality [9]. Concerns among users included contributing to antimicrobial resistance and impacts on microbiota.

Impact of doxy-PEP on bacterial STI incidence outside of clinical trial settings

Evidence from randomised clinical trials (RCTs) demonstrates that doxy-PEP is effective in reducing incident chlamydia and syphilis among individual users. In addition, emerging data from ecological studies and real-world clinical settings implementing doxy-PEP guidelines, suggest a potential impact at the clinic level and within communities of men who have sex with men.

In San Francisco, between November 2022 and November 2023, following the city-wide implementation of doxy-PEP guidelines for men who have sex with men and transgender women with a history of an STI and/or multiple sex partners in the past year, reported cases of chlamydia and early syphilis declined markedly. Compared with projected case numbers based on surveillance data, chlamydia cases declined by 49.6% (95% CI: –59.1% to –38.1%) from 13 280 projected cases to 6 694 observed cases. Similarly, early syphilis cases declined by 51.4% (95% CI: –58.2% to –43.5%) from 4 365 projected to 2 121 observed cases [43]. In contrast, gonorrhoea cases increased by 25.6% (95% CI: –0.4% to 58.3%) with 9 603 observed cases versus 7 650 projected cases. Doxy-PEP uptake among the key population groups was estimated at 19.5%, based on data from three sentinel STI clinics. Simultaneously, chlamydia cases increased among cisgender women, a group not included in the doxy-PEP guidelines.

In Northern California, among a cohort of HIV-PrEP users, 19.5% (2 253/11 551) received doxy-PEP between November 2022 and December 2023. Among doxy-PEP users, quarterly chlamydia positivity declined by 79% (from 9.6% to 2.0%; rate ratio [RR] 0.21, 95% CI: 0.16–0.27), syphilis by 80% (1.7% to 0.3%; RR 0.20, 95% CI: 0.11–0.37), and gonorrhoea by 12% (10.2% to 9.0%; RR 0.88, 95% CI: 0.77–1.00). STI rates remained stable among non-recipients, indicating (according to authors) significant real-world effectiveness of doxy-PEP [44].

At a sexual health clinic in Boston, Massachusetts, doxy-PEP was introduced in April 2023. Within the first year, 624/1 285 (48.6%) men who have sex with men and 15/57 (26.3%) transgender or nonbinary individuals attending the clinic received prescriptions. Over the first 12 months, doxy-PEP use was associated with a 54% decrease in chlamydia positivity (from 8.5% to 3.9%; RR 0.45, 95% CI 0.34–0.60) and a 42% decrease in syphilis positivity (from 2.4% to 1.4%; RR 0.59, 95% CI 0.37–0.96). No significant change was observed in gonorrhoea positivity (6.2% to 5.5%; RR 0.88, 95% CI 0.69–1.13) [45].

Reductions in chlamydia and early syphilis incidence in settings implementing doxy-PEP guidelines

Reports from settings that have implemented doxy-PEP guidelines focusing on men who have sex with men and transgender women with a history of STIs, indicate reductions in chlamydia and early syphilis incidence, both among doxy-PEP users and within local sexual networks of men who have sex with men. The limited or absent impact on gonorrhoea incidence, alongside the threat of antimicrobial resistance, highlights the need for additional STI prevention strategies, particularly for gonorrhoea.

Impact of using doxy-PEP on antimicrobial resistance

Evidence from randomised controlled trials on antimicrobial resistance among doxy-PEP users

Impact on STI pathogens

Among participants in RCTs, higher levels of tetracycline resistance were observed in incident gonorrhoea in those taking doxy-PEP versus those in the control group [7,9,46]. In the DoxyPEP trial, tetracycline resistance in *N. gonorrhoeae* isolates from doxy-PEP users was 27% (4/15) at baseline and 38% (5/13) during 12 months of follow-up. In the DOXYVAC study, *N. gonorrhoeae* isolates were all tetracycline resistant at baseline and during follow-up.

Surveillance data from King County, Washington, USA, covering 2017-2024, examined *N. gonorrhoeae* resistance trends among 2 312 men who have sex with men, following the introduction of doxy-PEP guidelines in Q2 2023. Tetracycline resistance was stable at about 27% from 2017 through Q1 2023, then rose sharply to 70% by Q2 2024 ($p<0.001$). High-level tetracycline resistance also increased significantly, from 2% in Q1 2021 to 65% in Q2 2024 ($p<0.0001$). Taking more than three doses of doxy-PEP per month was significantly associated with both tetracycline resistance and high-level tetracycline resistance ($p\leq0.01$ for both) [47].

There are concerns that doxy-PEP could lead to selection of resistance to other antibiotics (co-resistance). In the DOXYVAC study, the use of doxy-PEP was associated with a statistically significant increase in *N. gonorrhoeae* isolates showing high-level resistance to tetracycline along with decreased susceptibility to cefixime. This was observed in 32.3% (10/31) of isolates in the doxy-PEP arm vs 10.0% (4/40) in the control arm (p=0.033). Results were confirmed on additional nucleic acid amplification testing (NAAT) positive samples, with corresponding proportions of 22.2% (18/81) vs 6.5% (6/80) (p=0.014) [48]. Whole-genome sequencing revealed that isolates with decreased cefixime susceptibility had acquired a new mosaic penA allele (*penA34.007*), which was significantly more frequent in the doxy-PEP arm than the control arm (25.6% vs. 12.5%, p=0.045). The proportion of samples harbouring both tetM (conferring high-level tetracycline resistance) and *penA34.007* (associated with decreased susceptibility to extended-spectrum cephalosporins) was markedly higher in the doxy-PEP arm than in the control arm (22.2% vs 7.5%; p=0.014). This co-occurrence of *penA34.007* and tetM suggests that doxy-PEP may select for strains with multidrug resistance determinants, underlining the need for antimicrobial resistance surveillance and further research to assess implications of doxy-PEP use [48].

No phenotypic or genotypic markers of doxycycline resistance have been detected in *C. trachomatis* in any RCTs assessing doxy-PEP that looked for this [7,8,41]. In the DOXYVAC trial, no tetracycline resistance or resistance-associated mutations were detected in *C. trachomatis* strains from either study arm, including four strains tested in culture, and 68 of 126 PCR-positive swabs sequenced for 16S rRNA mutations. However, a tetracycline-resistant strain of *C. trachomatis* was obtained *in vitro* through horizontal transfer of the *tetC* gene, which confers tetracycline resistance from a *Chlamydia suis* strain that harbours this gene [49]. *Chlamydia suis*, which infects pigs, has gradually developed tetracycline resistance, which could be related to the indiscriminate use of tetracyclines in the agricultural industry [50].

None of the clinical trials assessed resistance in *Treponema pallidum.* To date, doxycycline resistance has not been reported in *T. pallidum;* however, tetracycline resistance due to mutations in the 16S rRNA gene could theoretically emerge [16,51].

Impact on other pathogens and commensals

In addition to the effects of doxy-PEP on resistance to tetracyclines among STI pathogens, there are concerns about increasing resistance among other bacteria. In the DoxyPEP study, resistance to doxycycline in *Staphylococcus aureus* isolated from nasopharyngeal or oropharyngeal samples increased in participants taking doxy-PEP from 12% at baseline, to 16% after 12 months; although the overall carriage declined from 45% to 28% [9]. A systematic review found that 24% of doxy-PEP users exhibited resistance in *S. aureus* samples, compared to 10% in the control group [52]. In a group of males eligible for doxy-PEP attending a clinic in Boston, USA, *S. aureus* tetracycline nonsusceptibility was associated with resistance to trimethoprim-sulfamethoxazole and clindamycin, leading the authors to conclude that doxy-PEP may select for resistance in *S. aureus* to multiple classes of antibiotics [53]. In the study from King County, Washington, USA, *S. aureus* colonisation was lower among doxy-PEP users compared with non-users (27% vs 36%, p=0.02), but tetracycline-resistant *S. aureus* was more common among doxy PEP users (18% vs 8%, *P* <0.0001%). In addition, colonisation with tetracycline-resistant Group A *Streptococcus* was more common among doxy-PEP users (9% vs. 4%, p=0.008, respectively) [47].

In the DOXYVAC study, methicillin-resistant *S. aureus* (MRSA) detection rates did not differ between the doxy-PEP and control arms over time [54].

In the DoxyPEP trial, oropharyngeal carriage of commensal *Neisseria* remained stable, but tetracycline resistance increased in the doxy-PEP group (63% to 70%, p=0.11) and decreased significantly in the control group (62% to 42%, p<0.01), suggesting doxy-PEP may contribute to resistance development in these bacteria [40].

In the DOXYVAC trial, the rate of detection of extended-spectrum β-lactamase producing *E. coli* in rectal swabs remained unchanged during follow-up in both groups [7].

Microbiome and resistome

Doxy-PEP may also affect the human microbiome. Reductions in the diversity of the gut microbiome have been linked to chronic diseases, such as diabetes and autoimmune diseases. In the DoxyPEP trial in the US, participants in the doxy-PEP arm displayed increased proportional abundance of tetracycline antimicrobial resistance genes (ARGs) in their gut resistome, and increased expression of ARGs at six months of follow-up. However, doxy-PEP had minimal impact on the gut microbiome's alpha and beta diversity or taxonomic composition [55]. In the Dual Daily HIV PrEP and STI PrEP (DuDHS) trial, conducted in Vancouver, Canada, 41 participants, including men who have sex with men and transgender women using daily HIV-PrEP, were enrolled in the microbiome sub-study [56]. Participants received daily doxycycline pre-exposure prophylaxis (doxy-PrEP), defined as 100 mg of doxycycline taken once daily, either immediately from baseline to week 48 or in a deferred manner starting at week 24 and continuing to week 48. Rectal microbiome analyses showed stable composition over 12 months, with no significant changes in taxa or diversity at the genus level. A slight (<10%) decrease in alpha diversity at the phylum level was observed in the immediate doxy-PrEP arm, indicating minimal overall impact of doxy-PrEP on the rectal microbiome. However, further research is needed to explore the impact of doxycycline for STI prevention on microbiome function and antimicrobial resistance.

Evidence indicates that doxy-PEP has an adverse impact on antimicrobial resistance in some bacterial pathogens, commensals and the human resistome

Data from clinical trials and surveillance studies in real-world settings implementing doxy-PEP guidelines show that its use is associated with increasing resistance to tetracyclines in *Neisseria gonorrhoeae*, including high-level resistance. Cross-resistance to other antibiotics in *Neisseria gonorrhoea* among doxy-PEP users has also been reported. Resistance to tetracyclines has not been observed in neither *C. trachomatis* nor *T.* pallidum. Among non-STI pathogens, doxy-PEP use has been linked to increased resistance in *Staphylococcus aureus,* Group A *Streptococcus,* and commensal *Neisseria*. Gut microbiome studies have found increased tetracycline resistance genes, without major changes in overall composition or diversity. Continued antimicrobial resistance surveillance and future research on long-term effects are needed.

Pre-existing high percentages of tetracycline resistance in *Neisseria gonorrhoeae* in the EU/EEA

EU/EEA surveys on tetracycline resistance in *N. gonorrhoeae* have documented high percentages of resistance, as reported by Unemo et al. [57] for 2022 and in the ECDC Euro-GASP report for 2023 isolates [57,58]. The 2022 European survey of 4 787 *N. gonorrhoeae* isolates from 19 EU/EEA countries found 63.4% tetracycline resistance (MIC>0.5mg/l), with 16 countries reporting rates above 30%, 11 above 50%, and seven above 70% resistance; overall, 13.3% isolates showed high-level plasmid-mediated resistance [57]. When repeated in 2023, with 3 014 isolates from 22 countries, the survey showed 58.4% resistance, similar to the 2022 level. Tetracycline resistance was higher among men who have sex with men (OR 1.96) and females (OR 1.37) compared to heterosexual males, and people over 25 years (OR 1.32) compared with those under 25 years. For the 2023 sample, 11.9% of isolates showed high-level plasmid-mediated resistance (MIC > 8 mg/L), with such strains detected in 20 out of 22 countries. Compared to 2023, the 2024 survey (3597 isolates from 22 countries) showed a significant rise in isolates, with MICs of 8–64 mg/L and a decline in those with lower MICs of 0.125–0.5 mg/L and 4 mg/L ($p<0.0001$ and $p<0.0008$) [59]. This suggests a shift toward high-level plasmid-mediated resistance and fewer susceptible strains.

While the risk of antimicrobial resistance appeared to be minimal among participants in two clinical trials (DoxyPEP, DOXYVAC), an assessment by Vanbaelen T et al. suggests the need for more refined methods to assess the potential of doxy-PEP among men who have sex with men to lead to increased resistance to tetracyclines [46].

Doxy-PEP is unlikely to reduce incident gonorrhoea in most EU/EEA settings

Considering the high percentages of tetracycline resistance in *Neisseria gonorrhoeae* across the EU/EEA, particularly among men who have sex with men compared with heterosexual populations, doxy-PEP is unlikely to reduce incident gonorrhoea in most EU/EEA countries. Furthermore, doxy-PEP could rapidly select for gonococcal strains with tetracycline resistance.

Current use of doxy-PEP and characteristics of people using it

The most recent EMIS survey was conducted in the first half of 2024, covering men who have sex with men and gender-diverse individuals in 50 countries, with 50 330 respondents [60]. Among other sexual health topics, EMIS-2024 explored the use of antibiotics, including doxycycline, for STI prevention, either as PEP or PrEP. The survey focused on respondents residing in EU/EEA countries who reported sex with non-steady male partners in the past 12 months (n = 31 566). Of the respondents, 8.4% reported using antibiotics for STI prevention (country median: 7.7%; range: 2.8% [Sweden] to 14.2% [France]).

Geographically, antibiotics use was more common in Western and Southern Europe (e.g. Belgium, Croatia, France, Portugal, Spain) and less common in Northern and Eastern Europe (e.g. Estonia, Finland, Norway, Sweden). Respondents obtained antibiotics through a variety of channels, including prescriptions from healthcare providers, leftover medication, over-the-counter pharmacy purchases, or online sources. Preventive antibiotic use increased steadily in line with the number of sexual partners an individual had, and the diversity of sexual practices, reaching up to 25% among those reporting more than 50 partners in the previous 12 months. Use was particularly high among men who have sex with men aged 35–39 years (11%), those diagnosed with HIV (14%), and those using HIV PrEP (16%).

The EMIS-2024 findings align with a 2024 online survey of 1 633 men who have sex with men, trans and gender-diverse people in the Netherlands [61], where 22.5% had used doxycycline for STI prevention and 15.1% had used it in the past six months. Recent users were more likely to be living with HIV, using HIV PrEP, and have multiple partners, use specific psychoactive substances to enhance sexual experience ('chemsex'), and engage in group sex. Most of these individuals used doxycycline intermittently (two to four times over six months), with

doxycycline being the primary antibiotic, though others such as azithromycin and ciprofloxacin were also used informally. Informal doxy-PEP/PrEP use (self-sourced) has risen significantly since a 2021–2022 survey among men who have sex with men in Amsterdam, where only 2.5% of 593 participants had ever used doxy-PEP before [62].

Survey data indicate that men who have sex with men who perceive themselves to be at increased risk of STIs are more likely to initiate doxy-PEP, which suggests there is doxy-PEP uptake among individuals most likely to benefit from it. Reported motivations include a strong desire to protect themselves and their partners, reduce STI transmission within their communities, and alleviate anxiety and stigma [61,63]. In a survey among 875 men who have sex with men and transgender women in Belgium in 2024, the respondents willingness to use doxy-PEP decreased from 80% to 60% after being briefed about the potential effects of doxy-PEP on antimicrobial resistance, and their concerns about side effects and AMR increased from 50% to 70%, indicating that informing patients about benefits and risks is crucial in supporting informed decision-making [64].

In 2024, ECDC launched its first survey to monitor national responses to the STI epidemic [35]. The survey included questions on: 1) the existence of national guidance, policy, or recommendations regarding doxy-PEP for the prevention of bacterial STIs; 2) whether healthcare providers prescribe doxy-PEP for prophylaxis regardless of official guidelines; and 3) any evidence of informal doxy-PEP use within the country. Of the 29 countries that responded, four (Austria, Czechia, Germany, and Ireland) reported having national guidance in place at the time of the survey, most of which advised on doxy-PEP for people at high risk of STIs, based on case-by-case decisions. Of 25 countries with no national guidance, nine indicated anecdotal or other evidence of prescriptions being issued. Additionally, 13 of the 29 countries that responded reported evidence of informal doxy-PEP use, citing sources such as STI clinicians, community organisations, and surveys.

Antibiotic prophylaxis use is common among men who have sex with men and gender-diverse individuals at higher risk of acquiring an STI in the EU/EEA

The use of antibiotics, including doxycycline, for STI prevention is common among men who have sex with men across the EU/EEA, with substantial variation across countries. Its prevalence is primarily influenced by the number of sexual partners people have and their sexual practices, and is particularly high among individuals accessing HIV care, including those using HIV pre-exposure prophylaxis. Access pathways range from healthcare provider prescriptions to self-sourcing, the latter of which is considerable. Unsupervised antibiotic use is a concern, reflecting the need for increased awareness of appropriate antibiotic use and its implications.

Impact of doxy-PEP on antibiotic consumption

Regarding the impact of doxy-PEP use on the consumption of other antibiotics, a study by Vanbaelen et al. suggested that doxy-PEP might reduce the use of ceftriaxone and azithromycin, albeit at the expense of significantly increased doxycycline consumption [46]. In line with this, a pre-post within-person analysis at a clinic in Milan, Italy, where doxy-PEP was prescribed between August 2022 and July 2024, showed reductions in chlamydia, gonorrhoea, and syphilis diagnoses [65]. Among 222 users, observed days of therapy (DOTs) per 1 000 person-days were considerably lower for doxycycline (3.21 vs. 24.71), benzylpenicillin (0.37 vs. 1.86), and ceftriaxone (1.26 vs. 4.85) compared to expected use without doxy-PEP.

An ECDC modelling exercise suggests that potential doxycycline use for doxy-PEP among men who have sex with men on HIV-PrEP in the EU/EEA could amount to approximately 4.3 million defined daily doses of doxycycline annually (95% credible interval (CrI): 0.5–17.4 million), representing a 1.84% increase in consumption compared to 2023 levels (95% CrI: 0.19–7.49%) [66]. Population size estimates were informed by EMIS-2024 and assumption on percentage of HIV-PrEP users that will also use doxy-PEP by expert elicitation.

Impact of doxy-PEP on syphilis diagnostics

A small case series in Italy suggests that doxy-PEP may delay early detection of syphilis by delaying seroconversion. In three men who have sex with men, serological tests (including treponemal antibody, rapid plasma reagin (RPR), and hemagglutination assays) remained negative or indeterminate for up to three weeks after ulcer onset [67]. These findings highlight the need to monitor and potentially adjust diagnostic algorithms for individuals using doxy-PEP. They may also affect the ability to meet the EU case definition for syphilis surveillance, which requires serological evidence of *T. pallidum* antibodies and additional confirmation through either a treponemal IgM assay or a non-treponemal test (e.g. RPR or VDRL) [68].

Considerations from a public health perspective

Across EU/EEA countries, existing clinical guidelines include doxy-PEP against bacterial STIs on a case-by-case basis, primarily targeting syphilis prevention among men who have sex with men at high risk of infection. Self-sourcing without medical prescription has also been documented. Recent data indicate increasing uptake and geographical expansion of doxy-PEP use among men who have sex with men across the EU/EEA [34,35,61]. There are also reports of other antibiotics (e.g. azithromycin, ciprofloxacin, amoxicillin) being used/misused with the intention of STI prevention in this group. These trends may reflect real or perceived unmet prevention needs among populations experiencing high bacterial STI incidence, as well as a need to streamline sexual health messaging to more clearly communicate the knowns and unknowns and the benefits and risks of antibiotic prophylaxis.

Evidence from RCTs and observational studies supports the effectiveness of doxy-PEP in reducing incident chlamydia and syphilis, at both individual-user level and within sexual networks of men who have sex with men with high prevalence of bacterial STIs. However, it is currently unknown how long these reductions will be sustained and whether this is an effective way to reduce prevalence in highly connected sexual networks [69]. These studies also indicate a potential for accelerating antimicrobial resistance development in bacterial pathogens and bystander organisms not only among doxy-PEP users, but also among non-users, including individuals within sexual networks, men who have sex with men, and potentially, other population groups.

In this context, it is important that national public health authorities have a good oversight of doxy-PEP use and monitor its public health impact. Where national recommendations or clinical guidelines are in place and healthcare providers are prescribing it, or where there is evidence for informal use, several key aspects should be considered from a public health perspective.

- Integrate doxy-PEP into comprehensive sexual health strategies.
  - Ensure that prescription of doxy-PEP is medically guided;
  - Promote informed decision-making;
  - Integrate doxy-PEP with other sexual health services;
  - Combine doxy-PEP with regular testing and monitoring;
  - Periodically reassess users' needs;
  - Promote awareness of antimicrobial resistance.
- Focus on syphilis prevention.
- Use doxy-PEP in groups where the risk of infection is highest.
  - Prioritise groups based on epidemiology;
  - Consider the needs of special populations;
  - Consider individual and event-driven risk profiles.
- Monitor public health impact.
  - Assess impact on antimicrobial resistance and consumption;
  - Assess impact on bacterial STI incidence;
  - Assess users' characteristics and needs over time.
- Engage communities and stakeholders.
  - Understand community perspectives;
  - Reach out to informal users.
- Ensure clear and up-to-date guidelines and provider and user education.
  - Develop and update national guidelines;
  - Ensure broad dissemination of guidelines;
  - Provide education and tools.

Integrate doxy-PEP into comprehensive sexual health strategies

- **Ensure that prescription is medically guided:** European survey data indicate that men who have sex with men with high sexual activity and who have multiple partners are more likely to self-select for doxy-PEP use. Self-sourcing is widespread across Europe, with an increasing west-to-east gradient. Medically guided doxy-PEP prescription, following national or international guidelines, is the preferred alternative.
- **Promote informed decision-making:** Individuals who are eligible for doxy-PEP according to national guidelines, or those requesting it, should be informed about the expected benefits and harms, as well as the uncertainties regarding long-term effects, including potential increases in antimicrobial resistance. This information should support shared decision-making between the potential user and the prescribing healthcare provider.
- **Integrate with other sexual health services:** Where offered, doxy-PEP should be part of a broader sexual health plan that includes health promotion, risk-reduction counselling, STI screening and treatment, vaccination (e.g. HPV, hepatitis A/B, mpox), and HIV PrEP, tailored to the individual's risk profile and in line with national guidelines.
- **Combine with regular testing and monitoring:** Individuals prescribed doxy-PEP should undergo STI testing in line with national guidelines (e.g. at baseline and every three to six months thereafter). HIV testing should be included for HIV-negative individuals, with referral to HIV PrEP and PEP services, as HIV-negative doxy-PEP users may be at risk for HIV. Side effects should be monitored.
- **Periodically reassess user's needs:** Where prescribed, the need for doxy-PEP should be reassessed every three to six months to ensure it remains appropriate for the individual's current risk-benefit balance. The importance of testing and early treatment, particularly for syphilis, should be emphasised, together with the possibility to lower the risk through safer sex practice.
- **Promote awareness on antimicrobial resistance:** Healthcare providers should inform doxy-PEP users about AMR risks at both personal and community levels. This includes encouraging the reduction of overall antibiotic consumption and clarifying the distinction between doxy-PEP and doxy-PrEP.

Focus on syphilis prevention

- Doxy-PEP should primarily be considered for syphilis prevention in individuals at high risk of acquiring syphilis, particularly in settings or groups with high prevalence or increasing incidence of syphilis. National guidelines define 'high-risk' based on sexual health history, including men who have sex with men and transgender women with previous syphilis infection, bacterial STIs in the past 12 months, recent and/or anticipated intense sexual activity such as 'chemsex', group sex, frequent partner exchange.
- Doxy-PEP may also reduce *C. trachomatis* infections. However, the direct clinical benefit among men who have sex with men may be limited given the low risk of complications associated with asymptomatic infections in men. While the majority of lymphogranuloma venereum (LGV) infections in the EU/EEA are reported among men who have sex with men and a benefit of doxy-PEP is plausible, the impact on LGV incidence has not been evaluated in RCTs.
- Considering the high percentages of tetracycline resistance in *Neisseria gonorrhoeae* across the EU/EEA, particularly among men who have sex with men compared with heterosexual populations, doxy-PEP is unlikely to reduce incident gonorrhoea in most EU/EEA countries. Furthermore, doxy-PEP could rapidly select for gonococcal strains with tetracycline resistance.

Use doxy-PEP in populations where the risk of infection is highest

The consensus statements from the Expert Advisory Group emphasised that doxy-PEP is not an intervention that is suitable for population-level intervention. Where decisions are made to implement doxy-PEP, some key considerations are suggested:

- **Prioritise populations based on epidemiology:** In the EU/EEA, epidemiological data indicate that men who have sex with men using HIV PrEP, those living with HIV, and those attending STI clinics are at high risk of bacterial STIs, including syphilis. Although evidence is less robust, men who have sex with men and transgender women with migrant status and those engaged in sex work are also at elevated risk, and may benefit.
- **Consider the needs of special populations**: Doxy-PEP may be a relevant prevention option for male sex workers based on biological plausibility, but there isn't specific trial evidence. Potential benefits may also extend to female sex workers. Use of doxy-PEP could be considered as post-exposure prophylaxis among people who have experienced sexual violence. Based on experience of differences in access to other public

health interventions such as HIV-PrEP, attention should be given to facilitating access among racial and ethnic minority groups.
- **Consider individual and event-driven risk profiles:** Prescribing doxy-PEP guided by a person-specific risk profile can facilitate access for individuals at high risk of infection who may not be explicitly identified through epidemiological data or prioritised in national guidelines. Additionally, a person's risk level may temporarily increase in relation to anticipated exposure (e.g. sex parties, group sex, festivals), in which case, event-driven prescription can be considered to support safe and medically supervised use.

Monitor public health impact

Assess impact of doxy-PEP on antimicrobial resistance and consumption

- **Carry out antimicrobial resistance monitoring:** Given the limited information about antimicrobial resistance development associated with doxy-PEP it is essential to monitor AMR trends in bacterial STI pathogens (e.g. *N. gonorrhoeae*, *C. trachomatis, M. genitalium, T. pallidum),* other pathogens (e.g. *S. aureus*, group A streptococci, *Shigella* spp.), commensals (e.g. *Neisseria* spp.), as well as across various microbiota sites and on the gut resistome.
- **Ensure laboratory capacity:** Laboratories should be equipped to perform AMR monitoring, including tests of cure and detection of doxycycline treatment failure in STI pathogens. Methods may include culture, metagenomics and whole genome sequencing to investigate breakthrough infections [70].
- **Integrate AMR surveillance into existing data collection:** Monitoring AMR related to doxy-PEP should preferably be integrated into existing national and European surveillance systems. For example, the Euro-GASP project coordinated by ECDC introduced surveys on tetracycline resistance in *N. gonorrhoeae* in 2023, and starting with the 2024 sample, data on antibiotic use for STI prophylaxis will be also collected.
- **Quantify doxycycline use for STI prophylaxis:** Where available, use national antibiotic consumption data to estimate doxycycline use for STI prophylaxis; monitor in relation to the amount of doxycycline/tetracycline use for other areas of human health. Prioritise groups with a high baseline of antibiotic use, such as men who have sex with men on HIV PrEP. The ECDC model for estimating doxycycline consumption among HIV PrEP users can serve as a reference.

Assess impact of doxy-PEP on bacterial STI incidence

- **Enhance STI surveillance quality and granularity:** Enhance monitoring of syphilis, chlamydia, LGV, and gonorrhoea among populations targeted for or using doxy-PEP. Incorporate new surveillance variables ('HIV PrEP' and 'STI prophylaxis') introduced by ECDC in 2024 into national surveillance to better describe trends. Consider doxy-PEP monitoring as part of STI surveillance objectives.
- **Integrate complementary data sources:** Collect data from STI clinics on chlamydia, gonorrhoea and syphilis diagnoses among doxy-PEP users. Establish a baseline level for comparison over time. A standardised protocol for monitoring the impact of doxy-PEP, which will draw data from clinical settings, has been commissioned by ECDC and is expected to be published in the second quarter of 2026.
- **Use evidence from research:** Draw on publications and reviews of STI prevalence in selected populations and monitor prevalence dynamics over time to inform policy and guidelines.

Assess the characteristics of people who use doxy-PEP and their needs over time

- **Characterise doxy-PEP users:** Collect data on demographics, sexual behaviour, HIV status, and HIV PrEP use, including source of access (prescribed or informal). This information can guide prioritisation and ensure doxy-PEP reaches those most likely to benefit. It can also inform health promotion and risk communication messages for different groups. Key data sources include the EMIS-2024 survey, sexual health clinics, community-based surveys, and online tools/apps.
- **Assess motivations and barriers:** Use surveys or existing data to identify drivers, obstacles, and user needs, informing targeted public health interventions and tailoring communication messages.

Engage communities and stakeholders

- **Engage communities:** Where national recommendations or clinical guidelines are in place, authorities are encouraged to engage with leaders from different communities, health policy advocates and peers. This can help ensure equitable access to doxy-PEP, particularly for those most likely to benefit.
- **Understand community perspectives:** Use surveys and research to assess awareness, attitudes toward doxy-PEP, and broader views on antibiotic use, particularly among men who have sex with men at high risk of

infection and sex workers. This is particularly important in countries where informal use is documented, and formal clinical guidelines are lacking.
- **Reach out to informal users:** Provide clear, tailored information to informal users, many of whom may not access healthcare, to support informed decision-making.

Ensure clear and up-to-date guidelines and provider and user education

- **Develop and update national guidelines:** National guidelines or position statements on doxy-PEP should be formulated and regularly reviewed and updated as new evidence becomes available.
- **Ensure broad dissemination of guidelines:** Existing guidelines should be shared with all categories of healthcare providers who may encounter individuals eligible for/requesting doxy-PEP, to ensure broad and equitable reach.
- **Provide education and tools:** Healthcare providers can benefit from practical materials (e.g. patient interview guidelines, dosing instructions, side-effect information, alternatives) to support informed decision-making. It is also important to offer guidance on using inclusive, non-stigmatising and affirming language when discussing sexual health with the population of focus. Leaflets or infographics should be available for clinic attendees. Many civil society organisations already offer online resources that summarise current evidence and present clear, accessible messages to keep communities informed (e.g. EATG). It is important that public health entities and community organisations collaborate to produce and disseminate clear, accurate information.

Limitations

This document draws on evidence from a rapid literature review, recent European surveys and expert opinion. Current findings indicate that doxy-PEP is effective in reducing the incidence of syphilis and chlamydia among users in the short term. However, significant gaps remain in the evidence base. These include uncertainties regarding the long-term impact of doxy-PEP on STI transmission dynamics, the full constellation of potential effects on antimicrobial resistance, and its effectiveness in populations not represented in published randomised controlled trials.

In particular, the implications for antimicrobial resistance are not yet fully understood and more research is needed. This includes the potential for selective pressure on commensal and pathogenic organisms, the emergence of tetracycline resistance, and possible cross-resistance with other antimicrobial classes, as well as the impact on human microbiome.

These considerations reflect the state of evidence and data available at the time of literature review and expert consultation. As the field continues to evolve rapidly, findings and recommendations may need to be updated accordingly. The national context and epidemiological situation should also be considered when assessing the relevance and applicability of the considerations presented.

Areas for research

Methodologically robust trials and, where appropriate, well-designed observational studies are needed to address remaining evidence gaps on doxy-PEP from a public health perspective. A key priority is understanding the population-level impact of doxy-PEP on antimicrobial resistance. This includes microbiota studies focused on tetracycline resistance genes in both commensal and pathogenic bacteria. Relevant organisms include *Neisseria spp., N. meningitidis, S. aureus*, Group A Streptococcus, and *Streptococcus pneumoniae* in the throat, and ESBL-producing *Escherichia coli* and *Shigella spp.* in the rectum.

Further research is needed to investigate the efficacy of doxy-PEP among women, particularly regarding prevention of infertility, pelvic inflammatory disease, and congenital syphilis, and among men who have sex with women. To ensure generalisability, future trials should adopt more inclusive designs and recruit more demographically diverse populations.

Robust, up-to-date estimates of burden of diseases of bacterial STIs and their economic impact are important to inform future decision-making. ECDC will consider including these estimates in the proposal for revised STI surveillance objectives and future workplan. Comparative analyses of national doxy-PEP guidelines and implementation models can help identify approaches that best support targeted public health outcomes. In collaboration with the expert group, a set of priority research questions have been identified for consideration by the broader research community. These are presented in Annex 4.

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Annex 1. Members of ECDC Expert Advisory Group on doxy-PEP

Name	Affiliation	Country	Competency area
Adam Shanley	MPOWER Ireland	Ireland	Civil society, observer in the STI Network Coordination Committee
Barbara Suligoi	Istituto Superiore di Sanità, Rome	Italy	Public health – STI Network epidemiology
Béatrice Bercot	Saint-Louis Hospital, Paris	France	AMR bacterial STIs, clinical trials doxy-PEP, Public health - STI Network microbiology
Birgit van Benthem	Centre for Infectious Disease Control, National Institute for Public Health and the Environment	Netherlands	Public health – STI Network epidemiology
Catharina Missailidis	Department of Infectious Diseases / Venhälsan, Södersjukhuset Stockholm	Sweden	Sexual healthcare/clinician
Christopher Kenyon	STI Unit, Institute of Tropical Medicine, Antwerp	Belgium	AMR bacterial STIs, human microbiome, sexual healthcare/clinician
Giovanni Villa	St. James's Hospital, Dublin	Ireland	Clinical trials doxy-PEP, sexual healthcare/clinician
Henry J. C. de Vries	Amsterdam University Medical Centres and Public Health Service of Amsterdam	Netherlands	Sexual healthcare/clinician, clinical trials doxy-PEP
Javier Gómez Castellá	Division for Control of HIV, STIs, viral hepatitis and tuberculosis. General Directorate of Public Health and Health Equity. Ministry of Health of Spain.	Spain	Policy making in the area of STIs
Jørgen Skov Jensen	Research Unit for Reproductive Microbiology, Bacteria, Parasites, and Fungi, State Serum Institute, Copenhagen	Denmark	AMR bacterial STIs, human microbiome
Klaus Jansen	Department for Infectious Disease Epidemiology, Robert Koch Institute	Germany	Public health – STI Network epidemiology, chair of STI Network
Magnus Unemo	WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro	Sweden	AMR bacterial STIs, human microbiome, Euro-GASP consultant
Maria Victoria Hernando Sebastián	HIV/STI/Hepatitis Surveillance Unit. National Centre for Epidemiology, Carlos III Health Institute, Madrid	Spain	Public health – STI Network epidemiology
Radu Botgros	Public Health Threats Department, European Medicine Agency	Netherlands	Public Health Threats Department, EMA
Ricardo Werner	Division of Evidence-Based Medicine (dEBM) and Consultant physician at Charité – Universitätsmedizin Berlin, Department of Dermatology, Venereology and Allergology.	Germany	Clinical trials doxy-PEP, sexual healthcare/clinician
Robert Hejzák	The European AIDS Treatment Group (EATG) Czech AIDS Help	Czechia	Civil society, observer in the STI Network Coordination Committee
Sorin Tiplica	International Union Against Sexually Transmitted Infection (IUSTI) Europe	Romania	Sexual healthcare/clinician, IUSTI Europe
Thibaut Vanbaelen	STI Clinic, Institute of Tropical Medicine, Antwerp	Belgium	Clinical trials doxy-PEP, sexual healthcare/clinician, AMR bacterial STI
Thomas Tängdén	Department of Infectious Diseases, Uppsala University Hospital Chair, Strama – The Swedish Strategic Programme Against Antibiotic Resistance	Sweden	broad AMR perspective
Viatcheslav Grankov	WHO Regional Office for Europe	Denmark	Public health – STI
Danica Valkovičová Staneková,	St. Elizabeth College of Health and Social work, Bratislava	Slovakia	Public health – STI Network microbiology
Eimear Brannigan	Antimicrobial Resistance and Infection Control Team, Health Service Executive (HSE) Dublin	Ireland	broad AMR perspective, AMR bacterial STIs, antimicrobial stewardship
Fiona Lyons	Sexual Health Programme Health Service Executive (HSE) Dublin	Ireland	Policy making in the area of STIs, sexual healthcare/clinician
Lindley Barbee	Division of STD Prevention; US Centers for Disease Control and Prevention (CDC)	USA	Public health – STI

Annex 2. Scoring and ranking of key topics for public health considerations by Expert Advisory Group

Prior to the first meeting of the Expert Advisory Group, in October 2024, ECDC identified several questions of public health relevance related to doxy-PEP. These questions were circulated to the group, who were invited to score each question based on its relevance to public health in the EU/EEA, using a scale from 1 (low relevance) to 3 (high relevance). In the table below, questions are sorted by average score.

Questions with potential public health relevance	Number of votes	Total score	Average
What would be the impact of doxy-PEP implementation on **AMR of bacterial STI pathogens** (e.g. *N gonorrhoea*, *Chlamydia trachomatis, Treponema pallidum*) - at individual (doxyPEP user) and population levels (community)?	17	49	2.9
What would be the impact of doxy-PEP implementation on **AMR of other pathogens** (e.g. *Staphylococcus aureus*) – at individual (doxy-PEP user) and population level (community)?	17	48	2.8
Which **populations** would mostly benefit from doxy-PEP implementation as a public health intervention in the EU/EEA?	17	44	2.6
What would be the impact of doxy-PEP implementation on **bacterial STIs incidence** in the general population and specific populations (on medium and long-term)?	17	42	2.5
What are the **key health promotion and risk communication** messages in relation to doxy-PEP for different groups, including users, healthcare providers, policymakers?	12	30	2.5*
How does the **amount of doxycycline** that is expected to be used for STI prevention among risk groups compares with the volume of doxycycline and other tetracyclines used in human and, potentially, animal health?	17	40	2.4
What would be the impact of doxy-PEP implementation on the **human microbiome**?	17	39	2.3
What will be the impact of doxy-PEP implementation on **STI diagnosis** among people taking doxy-PEP and their sexual contacts? *Will there be a need to update current guidelines?*	17	36	2.1
What is the effectiveness of doxyPEP in **non-RCT settings** (e.g. demonstration projects)?	16	34	2.1*
What are **users' characteristics** and their potential **needs**?	17	34	2.0
What is the **amount of doxycycline** that is expected to be used for implementing doxy-PEP for STI prevention among risk groups?	17	32	1.9
What is the **extent of current use** of doxy-PEP in EU/EEA?	17	30	1.8
What will be the impact of doxy-PEP implementation on the **management of sexual partners** of people taking doxyPEP? *Will there be a need to update current guidelines?*	15	24	1.6*

**Scores calculated based on a lower number of votes than 17.*

Annex 3. Guidelines, recommendations and statements

Guideline title, country, year of release	Target (eligible) group	Recommendation	Sexual health approach
CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024, CDC	Men who have sex with men or transgender women with syphilis, chlamydia, or gonorrhoea in past 12 months. Event-driven eligibility ("sexual activities that are known to increase the likelihood of exposure to STIs").	200 mg doxycycline within 72h after oral, vaginal, or anal sex. Max 200 mg per 24h. Shared decision-making process with the patient	Risk-reduction counselling, STI testing/treatment, vaccination, HIV-PrEP/care linkage. Bacterial STI testing at exposure sites every 3–6 months. Reassess doxy-PEP need and screen for HIV per guidelines.
Doxycycline en prévention des infections sexuellement transmissibles bactériennes France, 2025	Men who have sex with men, transgender women with at least two partners in the past 12 months, *and* at least two episodes of bacterial STIs (*C. trachomatis, N. gonorrhoeae, or T. pallidum*) in the past 12 months.	200 mg of doxycycline taken orally in a single dose ≤72h after condomless sex, max 3×/week. Off-label use. Not recommended routinely. Shared decision-making process with the patient.	Risk-reduction counselling, HIV/STI screening every 3 months, STI treatment per guidelines, STI vaccination, HIV-PrEP. Follow-up: Test of cure to monitor for doxycycline-resistant STIs.
DOCUMENTO DE POSICIONAMIENTO SOBRE EL USO PROFILÁCTICO DE DOXICICLINA PARA PREVENIR LAS ITS (DOXI-PEP) Spain, 2024	On individual basis for men who have sex with men or transgender women who have sex with men and have experienced repeated STIs in the past year.	Doxy-PEP (200 mg/day) taken as soon as possible after oral, anal, or vaginal sex without a condom- ideally within the first 24 hours, and never later than 72 hours. Routine use not recommend.	Regular STI screening (every 3 months). Risk-reduction counselling, HIV-PrEP where appropriate.
Position Statement of the German STI Society (Deutsche STI Gesellschaft, DSTIG): Antibiotic STI Prevention with Doxycycline (Doxy-PEP/Doxy-PrEP) Germany, 2023	*Necessary criteria:* men who have sex with men or transgender women on/eligible for PrEP or with HIV. *Plus ≥1 of:* recurrent syphilis; multiple STIs (6 mo); ≥10 male partners (6 mo); chemsex, group sex, sex-positive parties; or frequent partner change	Doxycycline 200mg orally within 24 hours after sex, on a case-by-case basis. DSTIG against widespread implementation. Off-label use; therefore, user pays. Prescriber holds legal responsibility.	
Doxy post-exposure prophylaxis for STI not endorsed by BREACH Belgium, 2023	Individual level prescription in medically supervised settings and preferably in a research context.		
UK National Guideline for the Use of Doxycycline Post Exposure Prophylaxis (DoxyPEP) for the Prevention of Syphilis UK BASHH, 2025	Cisgender gay, bisexual and men who have sex with men and transgender women at elevated risk of acquiring syphilis. Cisgender gay, bisexual and men who have sex with men and transgender women with concurrent male and cisgender female or other partners with a womb and ovaries. People assigned female at birth at elevated risk of acquiring syphilis (this may include sex workers and transgender men who have sex with men). People at elevated risk of acquiring syphilis attending for clinical care within 72 h of sexual assault.	200 mg of doxycycline, within 24 hours and no later than 72 hours after sex	Comprehensive approach to STIs prevention: condoms, HIV-PrEP/PEP, vaccination, testing, treatment, risk reduction, mental health support. If doxy-PEP users are: • Syphilis contact: offer epi treatment; • Symptomatic gonorrhoea/M. gen: manage per BASHH; • Asymptomatic chlamydia contact: no treatment if doxyPEP <72h; test if in clinic. Report doxy-PEP use for public health surveillance purposes.
Preexpoziční profylaxe HIV (PrEP) a postexpoziční profylaxe HIV (PEP) Profylaxe jiných sexuálně přenosných chorob, Doxy-PEP Czechia, 2024	On a case-by-case basis for individuals with recurrent STIs. Men who have sex with men and transgender women with at least one bacterial STI in the past 12 mo. Also for those without recent STIs, but planning high-risk sexual activity.	Dose: 200 mg doxycycline Timing: Within 24h (max 72h) after condomless sex Limit: Max 1 dose/24h, 4 doses/week	Initial visit: STI screening/treatment, risk-reduction counselling, doxy-PEP risks/benefits discussion, usage instructions. Follow-Up: STI screening (3–6 mo), monitor side effects, reassess need, renew prescription.
Stellungnahme der Österreichischen AIDS Gesellschaft (ÖAG) und Österreichischen Gesellschaft für STD und dermatologische Mikrobiologie (ÖGSTD) zum Einsatz der DOXY-PEP Austria, 2024	Men who have sex with men/transgender women with HIV or on PrEP. High STI risk (STI in past 6 mo, chemsex, >10 partners in 6 mo). Case-by-case decision. Prescribed only by HIV/PrEP/STI specialists.	200 mg within 24 to 72h after sexual intercourse. Off-label use.	Monitoring AMR (especially in gonococci) essential.

Guideline title, country, year of release	Target (eligible) group	Recommendation	Sexual health approach
ZASADY OPIEKI NAD OSOBAMI ŻYJĄCYMI Z HIV ZALECENIA PTN AIDS 2025 Poland, 2025	HIV-PrEP users. Recommended individually to patients based on risk assessment.	200 mg within 72 h after condomless sex.	
Nederlandse stellingname inzake doxyPEP december 2024 Netherlands, 2025	DoxyPEP use is discouraged. May be considered only for men who have sex with men/transgender women at high syphilis risk who already use or request it. Use should be time-limited and reassessed.	200 mg doxycycline within 24-72 hrs after unprotected sex. Note that this is off-label use; record patient consent.	Provide counselling on correct use, STI testing, and PrEP. Test per standard protocols; include gonorrhoea culture. If syphilis suspected, stop doxy-PEP, perform NAAT and serology, repeat in 2 weeks if negative.

NAAT: nucleic acid amplification test; mo: month

Annex 4. Research questions identified together with the ECDC Expert Advisory Group

- What is the impact of doxy-PEP on STI diagnoses among users and their sexual contacts?
- How does doxy-PEP affect the management of sexual partners of individuals using it?
- Should STI testing approaches be revisited for different population groups? Are current testing strategies identifying infections that may not be clinically relevant to the host or their contacts?
- How might doxy-PEP alter the clinical presentation and diagnosis of syphilis? For example, is a one-titre increase in rapid plasma regain significant if doxy-PEP has been taken more than ten times in the preceding month?
- What are the effects of doxy-PEP on colonisation resistance?
- How does doxy-PEP influence attitudes and practices around antibiotic stewardship?
- What methods can be developed to assess the population-level impact of doxy-PEP? How can benefits and risks be weighed to support evidence-informed decision-making?
- Are there legal or policy barriers to implementing doxy-PEP?
- At what level of antimicrobial resistance in STI or other pathogens would decision-makers reconsider recommending doxy-PEP? Conversely, at what level of STI incidence reduction would discontinuing doxy-PEP be justified?
- What is the willingness to use doxyPEP among key populations (e.g., men who have sex with men, sex workers, transgender people)?
- What are the barriers and facilitators to initiation and adherence to doxy-PEP?
- What are community preferences for dosing schedules, delivery models, and settings?
- How can culturally sensitive information about doxy-PEP be effectively communicated to key populations?
- How effective are community-led interventions for education, distribution, and support?

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