

GUIDELINE

Position statement of the German STI Society on the prophylactic use of doxycycline to prevent STIs (Doxy-PEP, Doxy-PrEP)

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Summary

Over the past two decades, there has been a rise in the incidence of syphilis, particularly among men who have sex with men (MSM). This has sparked interest in studying the prophylactic use of doxycycline to prevent syphilis and other sexually transmitted infections (STIs), commonly referred to as Doxycycline Pre- or Post-Exposure Prophylaxis (Doxy-PrEP, Doxy-PEP). At the same time, demand from potential users for this preventive measure is increasing.

Several randomized controlled trials have demonstrated that the prophylactic use of doxycycline in MSM and trans women using HIV pre-exposure prophylaxis (HIV-PrEP) or living with an HIV infection effectively reduces the risk of syphilis and chlamydia infections. At present, however, unresolved questions remain, particularly regarding implications of a broad implementation of prophylactic doxycycline to prevent STIs on tetracycline and other antimicrobial resistance in bacterial STIs, non-STI-related bacterial pathogens, and the microbiome.

In response to the increasing demand and the challenge of balancing effectiveness, safety, and the risk of promoting antibiotic resistance, the German STI Society (DSTIG) has issued a position statement, providing specific recommendations regarding potential indications, criteria, and occasions for the use of doxycycline in STI prevention. These recommendations are based on current evidence and expert opinion.

SUMMARY AND RECOMMENDATIONS

Given the rising incidence of syphilis over the past 20 years in Germany and other countries, particularly among men who have sex with men (MSM), there has been an increasing body of evidence and demand for the preven-

tive use of the antibiotic doxycycline to avoid syphilis and other sexually transmitted infections (STIs). The preventive intake of doxycycline before, during, or after sexual exposure is internationally referred to as “doxycycline Pre- or Post-Exposure Prophylaxis (Doxy-PrEP/-PEP).” To promote terminological clarity, Doxy-PrEP/-PEP is referred to as

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“antibiotic STI prevention” in this position statement of the German STI Society (Deutsche STI-Gesellschaft, DSTIG).

The individual benefit of antibiotic STI prevention with doxycycline in terms of reducing the risk of syphilis and chlamydia infections has been convincingly demonstrated in several randomized controlled studies for MSM and transgender women using HIV PrEP or with known HIV infection. However, a Kenyan study did not prove effectiveness for cisgender women. Data on the population-level effects of antibiotic STI prophylaxis are currently only available from modelling studies, in which important factors such as a stratification by the number of sexual partners have been inadequately considered. To a large extent, the effects found in modelling studies, such as a reduction in the population-level syphilis incidence, depend on the nature and scope of the implementation of antibiotic STI prevention.

Doxycycline is a well-established and relatively well-tolerated antibiotic that is widely used for the treatment of infectious and non-infectious diseases, sometimes over weeks to months. Risks at the individual level include adverse effects of doxycycline (e.g., gastrointestinal adverse effects, phototoxicity, allergic reactions) and potential negative effects on the microbiome and body weight with frequent intake. Adverse effects at the individual level are considered to be low to moderate.

However, the possible effects of a widespread implementation of preventive doxycycline intake on tetracycline resistance in bacterial STIs, as well as bacterial pathogens outside the STI spectrum and microbiome bacteria, remain largely unclear. The data available from existing studies on this question are not sufficient to draw a clear conclusion.

Balancing needs, efficacy, safety, and the risk of promoting antibiotic resistance, DSTIG recommends that the preventive use of doxycycline should be reserved for selected individuals in selected situations. At present (data as of April 10, 2023), the following recommendations can be made:

- *Due to the unclear effects of such a strategy on antimicrobial resistance, DSTIG recommends against any broad implementation of antibiotic STI prevention, such as the general use of preventive doxycycline in sexually active individuals.*
- *The use of antibiotic STI post-exposure prophylaxis (Doxy-PEP, i.e., doxycycline 200 mg orally taken within 24 hours after sex) can be considered on a case-by-case basis. Criteria for making individual decisions and defining risk events or occasions for intake are outlined in Table 1. It is important to note that this is an off-label use outside the approved indication; in Germany the cost of the prescription is therefore to be borne by the individual concerned, and the prescribing physician bears the legal responsibility.*
- *DSTIG recommends against the continuous (daily) preventive intake of doxycycline (Doxy-PrEP) as a form of the antibiotic STI prevention.*

- *From the perspective of DSTIG, there is a need for research into the effects of antibiotic STI prevention on the spread of antibiotic resistance determinants and the development of antimicrobial effectiveness within bacterial pathogens. This includes pathogens such as *Treponema (T.) pallidum* and *Chlamydia trachomatis* (Serovars D-K and L1-L3), as well as bacterial pathogens outside the STI spectrum. Furthermore, potential changes in the microbiome at the individual patient level, taking into consideration the development of resistance, need to be investigated.*
- *The implementation of antibiotic STI prevention should not come at the expense of established preventive measures. In particular, regular syphilis testing, recommended at least every 6 months for MSM,^{1,2} or every 3 months with increased risk,³ remains crucial to effectively prevent long-term harm among at-risk groups and individuals.*

INTRODUCTION

Due to its relatively good tolerability, the anti-inflammatory antibiotic doxycycline, a second-generation tetracycline, is used for a wide range of bacterial infections and non-infectious diseases. Its areas of application include the treatment of acute bacterial infections and a broad use in the treatment of inflammatory skin conditions such as acne,⁴ rosacea,⁵ and bullous pemphigoid,⁶ as well as in Switzerland, France, and the Anglo-American region, for malaria prophylaxis.⁷

Doxycycline is also used in the treatment of various sexually transmitted infections (STIs) as a first- or second-line therapy, for example, in the treatment of *Chlamydia* infections⁸ and syphilis.⁹

Given the rising syphilis incidence over the past 20 years in Germany and other countries, doxycycline is increasingly used off-label by individuals at risk to prevent syphilis and other STIs.^{10–13} This approach constitutes chemoprophylaxis against STIs using doxycycline, for which the term “Doxycycline Pre- or Post-Exposure Prophylaxis (Doxy-PrEP/-PEP)” has become common. To promote terminological clarity, Doxy-PrEP/-PEP is referred to as “antibiotic STI prevention” within the present position statement. In Germany, there is a growing demand for the prescription of doxycycline to prevent STIs, according to the experiences of HIV specialists and STI practitioners. In a survey among PrEP users and people living with HIV (PLWH) conducted by the German AIDS Federation (Deutsche Aidshilfe, DAH) in 2020, 13% of respondents indicated that they occasionally or regularly used preventive antibiotics, and an additional 42% (PrEP users) or 25% (PLWH) expressed a general interest in antibiotic STI prevention (Deutsche Aidshilfe, personal communication A. J. Schmidt).

In the history of medicine, there have been numerous attempts to use antimicrobial substances for the prophylaxis of bacterial STIs, but so far, without success. However,

TABLE 1 Criteria that can be used in individual decisions as a basis for prescribing and using doxycycline to prevent sexually transmitted infections.

Criteria for prescribing and using doxycycline to prevent STIs	
Necessary criteria	1) <ul style="list-style-type: none"> - Men who have sex with men (MSM) or - Trans women who have sex with men 2) <ul style="list-style-type: none"> - Concurrent use or indication for use of HIV PrEP or - Known HIV infection
Additional criteria, examples	<ul style="list-style-type: none"> - Recurrent syphilis infections - Multiple other (symptomatic) bacterial STIs in the past six months - Sex with ten or more male partners in the past six months - Stimulant use during sex (“chemsex”, e.g., crystal meth, GHB/GBL, ketamine, mephedrone) - Group sex
Risk events/occasions, examples	<ul style="list-style-type: none"> - Participation in group sex - Participation in sex-positive parties with multiple sexual partners - Sex with multiple partners within a short time frame

Explanation: According to DSTIG, both “necessary criteria” and at least one “additional criterion” should be met for the prescription of antibiotic STI prevention. The “additional criteria” and the definition of “risk events/occasions” are consensus-based examples. Therefore, they are exemplary in nature and can be supplemented or expanded upon based on the physician’s assessment of individual risk.

Abbr.: STI, sexually transmitted infection.

TABLE 2 Matrix for the systematic assessment of potential benefits and risks of using doxycycline to prevent sexually transmitted infections.

	Individual level	Population level
Potential Benefits	<ul style="list-style-type: none"> - Reduction of the risk of sexually transmitted infections (STIs), especially syphilis and chlamydia infections - Improved quality of life, carefree sex 	<ul style="list-style-type: none"> - Reduction in syphilis incidence - Reduction in the incidence of chlamydia infections
Potential Risks	<ul style="list-style-type: none"> - Short- and long-term adverse effects - Undesirable immunological effects - Alteration of the gastrointestinal microbiome 	<ul style="list-style-type: none"> - Promotion of antimicrobial resistance in bacterial STIs - Promotion of antimicrobial resistance in bacterial pathogens in general

there is an increasingly extensive body of evidence from high-quality randomized controlled trials to assess the effectiveness and safety of antibiotic STI prevention with doxycycline.

In the following sections, based on the currently available evidence (as of April 10, 2023), the German STI Society (Deutsche STI Gesellschaft, DSTIG) provides an assessment of the benefits and risks of taking doxycycline as a preventive health intervention for individuals at high risk of syphilis and other sexually transmitted infections. To systematically assess benefits and risks, the matrix presented in Table 2 is used.

DEFINITIONS AND CLARIFICATION OF TERMINOLOGY

Doxy-PEP/-PrEP: Definitions and mode of use

The term Doxy-PEP/-PrEP refers to the preventive intake of doxycycline before, during, or after sexual risk events,

without having had an exposure to a person with a diagnostically confirmed syphilis or other STI (see also Section “Differentiation from prophylactic treatment after exposure to confirmed syphilis”).

In studies, both the intake of doxycycline *after* risk events (Doxy-PEP) and *continuous (daily)* intake (Doxy-PrEP) have been examined. In the case of Doxy-PEP, a single dose of doxycycline 200 mg is taken within 24 to a maximum of 72 hours after a risk event.^{14–16} Condomless sex was typically defined as the risk event or occasion for intake in randomized studies on Doxy-PEP. Doxy-PrEP refers to the continuous intake of doxycycline 100 mg daily to prevent the acquisition of an STI.^{17,18}

To promote terminological clarity, within this position statement, Doxy-PrEP/-PEP is referred to as antibiotic STI prevention with doxycycline.

Participants in most currently available randomized studies on the effectiveness of antibiotic STI prevention were MSM and, in some cases, transgender women who reported having sex with men.^{14–18} These study participants either used HIV PrEP concurrently or had a known HIV infection.

In contrast to the aforementioned studies, another randomized controlled study that included cisgender women in Kenya did not demonstrate effectiveness of antibiotic STI prevention in relation to *Chlamydia trachomatis* and *Neisseria (N.) gonorrhoeae* infections.^{19,20}

Differentiation from prophylactic treatment after exposure to confirmed syphilis

It is important to differentiate antibiotic STI prevention from partner treatment after sexual contact with a person in whom early syphilis has been diagnostically confirmed. This approach is recommended in the current syphilis guidelines in Germany (“In the case of relevant pathogen contact, a prophylactic treatment should be offered analogous to the treatment of early syphilis”; translation by the authors).⁹ The present position statement by the DSTIG explicitly does not address prophylactic treatment after contact with individuals with diagnostically confirmed syphilis or other STIs but solely focuses on the preventive use of doxycycline in individuals at high risk of exposure to sexually transmitted pathogens.

Differentiation from HIV pre-exposure prophylaxis (HIV-PrEP)

Furthermore, it is important to clarify the terminology in relation to HIV pre-exposure prophylaxis (HIV PrEP). HIV PrEP refers to the preventive intake of antiretroviral agents to prevent HIV infections in individuals at substantial risk of HIV infection. HIV PrEP is an established biomedical prevention measure not discussed in the present position statement.

BENEFITS AND RISKS OF ANTIBIOTIC STI PREVENTION

As of April 10, 2023, five randomized controlled trials (RCTs) have been published^{14–18} on antibiotic STI prevention with doxycycline in MSM, and in some instances, transgender women. An additional study^{19,20} investigated antibiotic STI prevention with doxycycline in cisgender women.

The five RCTs^{14–18} in MSM and, in some of these studies, in transgender women who reported having sex with men, comprised a total of 1,370 participants. All of these were either concurrently using HIV PrEP or had a confirmed HIV infection. Various additional criteria, such as a minimum number of sexual partners or a history of STIs, were frequently established. An overview of the study characteristics of these studies can be found in Table 3.

The subsequent sections will present the current evidence on the efficacy and safety of antibiotic STI prevention with doxycycline in MSM and transgender women.

In contrast to the studies mentioned before, an RCT conducted in Kenya on antibiotic STI prevention with doxycycline in cisgender women did not demonstrate significant effects in reducing Chlamydia infections and gonorrhoea.^{19,20} Results from this study are not included in the following sections.

Benefits of antibiotic STI prevention at the individual level

The effectiveness of antibiotic STI prevention has been investigated in terms of reducing the incidence of syphilis (Table 4), *Chlamydia trachomatis* infections (Table 5), gonorrhoea (Table 6), and bacterial STIs as a combined endpoint (Table 7). A reduction in the incidence among users of antibiotic STI prevention with doxycycline was seen for all outcomes, albeit to varying degrees.

The incidence of syphilis was reduced in all included studies^{14–18} among participants using preventive doxycycline (Table 4), with relatively homogeneous effect estimates. The reduction compared to control groups ranged from 73% to 87%.^{14–17} In one study, participants with confirmed HIV infection were analyzed separately from PrEP-using participants,¹⁶ and in one pilot study, only participants with HIV infection were included.¹⁷ Although the reduction in syphilis incidence was also substantial among PLWH (73% and 77%), it was not statistically significant in this subgroup. It is important to consider the small sample size in the study by Bolan et al.¹⁷ In one study¹⁸ for which no effect estimate was calculated, the incidence of syphilis decreased from 8.2 to 0 per 100 observed person-years (not statistically significant due to a low number of syphilis diagnoses). In all other studies^{14,15} as well as among PrEP users in the study mentioned above,¹⁶ the reduction in syphilis incidence was statistically significant.

The incidence of *Chlamydia trachomatis* infections was also significantly reduced in all included studies^{14–18} among participants using preventive doxycycline compared with controls (Table 5). Likewise, the effect estimates were relatively homogeneous, with the reduction in incidence ranging from 70% to 89%.^{14–16} In terms of *Chlamydia* infections, the reduction was statistically significant, regardless of whether the study participants were PrEP users or PLWH. In one study¹⁸ for which no effect estimate was calculated, the incidence of *Chlamydia* infections decreased from 81.6 to 0 per 100 observed person-years ($p = 0.001$). None of the aforementioned studies differentiated between the *Chlamydia trachomatis* serovars D-K and L1-L3. While conclusions can reasonably be drawn regarding the incidence of infections with *Chlamydia* serovars D-K, there is no evidence to assess the efficacy of preventive doxycycline against serovars L1–L3 *Chlamydia* infections. The available data likely apply to the more common serovars D-K, and specific information on serovars L1–L3 may be lacking in these studies. Additional research and data are needed to

TABLE 3 Overview of characteristics of randomized controlled trials on antibiotic STI prevention with doxycycline in MSM and transgender women.

Study	Study characteristics	Inclusion criteria and definition of risk events/occasions to use doxycycline	Interventions	Participants and follow-up	Comments
Bolan et al. (2015) ¹⁷	Open-label RCT; USA (Los Angeles)	MSM or transgender women with HIV infection and at least two diagnoses of syphilis since the diagnosis of HIV infection	Continuous intake of doxycycline 100 mg/day Financial compensation for STI-free status	15 participants, intake for 36 weeks, evaluation after 48 weeks 15 participants, 48 weeks	Pilot study, not designed in terms of study size to demonstrate statistically significant differences
Molina et al. (2018) ¹⁴	Open-label RCT, embedded in an HIV-PrEP cohort study; France (Paris, Lyon, Nizza, Tourcoing, Nantes)	HIV-negative MSM or transgender women using HIV PrEP <i>Risk event:</i> Unprotected anal or oral sex	Taking doxycycline 200 mg within 24 to a maximum of 72 hours after risk events	116 participants, 10 months	
Grennan et al. (2021) ¹⁸ , Tattersall et al. (2020) ²¹ ; „DuDHS trial“	Open-label RCT, participants were HIV-PrEP users; Canada (Vancouver)	HIV-negative MSM using HIV PrEP, with at least one syphilis infection before study enrolment	Control group Continuous intake of doxycycline 100 mg/day	116 participants, 10 months 26 participants, 24 weeks	Only conference abstracts available, a pilot study to evaluate feasibility
Luetkemeyer et al. (2023) ¹⁶	Open-label RCT; USA (Seattle, San Francisco)	MSM or transgender women using HIV PrEP or with known HIV infection and at least one diagnosis of syphilis, gonorrhoea, or chlamydia in the year before study enrolment. <i>Risk event:</i> condomless sex.	Control group Taking doxycycline 200 mg within 72 hours after risk events	26 participants, 24 weeks 374 participants, 189 PY of follow-up; 240 HIV-PrEP users, 134 with known HIV infection	Due to the effectiveness of the intervention, the study was prematurely terminated by the review board
Molina et al. (2023) ¹⁵	Open-label RCT, 2 × 2-factorial design (doxycycline, Meningococci B vaccination); France	MSM using HIV PrEP with a history of at least one STI in the year before study enrolment. <i>Risk event:</i> Condomless sex.	Control group Taking doxycycline 200 mg within 72 hours after risk events	180 participants, 82 PY of follow-up; 120 HIV-PrEP users, 60 with known HIV infection 332 participants; up to 96 weeks of follow-up, 9 months median follow-up (both groups).	Only conference abstract and presentation available; due to the effectiveness of the intervention, the review board recommended terminating the study prematurely
			Control group	170 participants; up to 96 weeks of follow-up, 9 months median follow-up (both groups).	

Abbr.: MSM, men who have sex with men; PY, person years; RCT, randomized controlled trial; STI, sexually transmitted infection

TABLE 4 Data from randomized controlled trials on the effectiveness of antibiotic STI prevention with doxycycline in reducing syphilis incidence.

Study	Mode of intake	Incidence in control group	Incidence in intervention group	Effect estimate
Bolan et al. (2015) ¹⁷	100 mg daily	7/49 visits (14.3%)	2/53 visits (3.8%)	OR 0.27 (95% CI: 0.04–1.73), p = 0.16
Molina et al. (2018) ¹⁴	200 mg p.e.	12.9/100 PY	3.7/100 PY	HR 0.27 (95% CI: 0.07–0.98), p = 0.047
Grennan et al. (2021) ¹⁸ , „DuDHS trial“	100 mg daily	8.16/100 PY	0/100 PY	p = 0.98
Luetkemeyer et al. (2023) ¹⁶	200 mg p.e.	7/257 quarterly visits (2.7%), MSM on PrEP	2/570 quarterly visits (0.4%), MSM on PrEP	RR 0.13 (95% CI: 0.03–0.59), p = 0.008
		3/128 quarterly visits (2.3%), MSM with known HIV infection	2/305 quarterly visits (0.7%), MSM with known HIV infection	RR 0.23 (95% CI: 0.04–1.29), p = 0.095
Molina et al. (2023) ¹⁵	200 mg p.e.	16.3/100 PY	3.4/100 PY	aHR 0.21 (95% CI: 0.09–0.47), p < 0.001

Explanation: The table presents data on the effectiveness of antibiotic STI prophylaxis with doxycycline regarding the reduction of syphilis incidence obtained from randomized controlled studies that included men who have sex with men (MSM) and, in part, trans women.

Abbr.: aHR, adjusted Hazard Ratio; HR, Hazard Ratio; OR, Odds Ratio; p.e., post exposure; PY, person-years; RR, Risk Ratio

TABLE 5 Data from randomized controlled trials on the effectiveness of antibiotic STI prevention with doxycycline in reducing the incidence of *Chlamydia trachomatis* infections.

Study	Mode of intake	Incidence in control group	Incidence in intervention group	Effect estimate
Molina et al. (2018) ¹⁴	200 mg p.e.	28.6/100 PY	8.7/100 PY	HR 0.30 (95% CI: 0.13–0.70), p = 0.006
Grennan et al. (2021) ¹⁸ , „DuDHS trial“	100 mg daily	81.63/100 PY	0/100 PY	p = 0.001
Luetkemeyer et al. (2023) ¹⁶	200 mg p.e.	31/257 quarterly visits (12.1%), MSM on PrEP	8/570 quarterly visits (1.4%), MSM on PrEP	RR 0.12 (95% CI: 0.05–0.25), p < 0.001
		19/128 quarterly visits (14.8%), MSM with known HIV infection	12/305 quarterly visits (3.9%), MSM with known HIV infection	RR 0.26 (95% CI: 0.12–0.57), p < 0.001
Molina et al. (2023) ¹⁵	200 mg p.e.	19.3/100 PY	2.1/100 PY	aHR 0.11 (95% CI: 0.04–0.30), p < 0.001

Explanation: The table presents data on the effectiveness of antibiotic STI prophylaxis with doxycycline regarding the reduction of the incidence of *Chlamydia trachomatis* infections obtained from randomized controlled studies that included men who have sex with men (MSM) and, in part, trans women.

Abbr.: aHR, adjusted Hazard Ratio; HR, Hazard Ratio; p.e., post exposure; PY, person-years; RR, Risk Ratio

assess the efficacy of preventive doxycycline for these less common serovars.

In terms of the incidence of gonorrhoea, a reduction was observed in all studies,^{14–17,21} but the data were much more heterogeneous compared to the reduction in syphilis and chlamydia incidence (Table 6). The reduction in gonorrhoea incidence ranged from 17% to 57%,^{14–16} and it was statistically significant in only some studies.^{15,16} In one study,¹⁸ for which no effect estimate was calculated, the incidence of gonorrhoea decreased from 57.1 to 31.4 per 100 person-years (p = 0.505). The variability in the effects on reducing *Neisseria gonorrhoeae* infections can be explained by the regionally varying susceptibility of gonococci to tetracyclines. The current resistance situation for *Neisseria gonorrhoeae* is monitored in Germany through a surveil-

lance project (GO-Surv-Stat, formerly GORENET) at the Robert Koch Institute (RKI) in Germany. Continuous surveillance data have been available for tetracyclines, and thus for doxycycline, since 2018. Given the widespread resistance against tetracyclines in Germany (78%–91% in the years 2018–2022), these antibiotics cannot be recommended for the treatment of gonorrhoea. In Germany, currently less than 10% of gonococcal isolates are sensitive to tetracyclines (2022: 8.8%).²²

Consistent with the data mentioned above on the reduction in the incidence of individual pathogens, a reduction in the *incidence of the combined outcome of infection with at least one of the measured bacterial STI pathogens* was observed (Table 7).^{14–18} In the study by Molina et al. (2023),¹⁵ only syphilis and chlamydia infections were

TABLE 6 Data from randomized controlled trials on the effectiveness of antibiotic STI prevention with doxycycline in reducing the incidence of gonorrhoea.

Study	Mode of intake	Incidence in control group	Incidence in intervention group	Effect estimate
Molina et al. (2018) ¹⁴	200 mg p.e.	34.5/100 PY	28.7/100 PY	HR 0.83 (95% CI: 0.47–1.47), p = 0.52
Grennan et al. (2021) ¹⁸ , „DuDHS trial“	100 mg daily	57.14/100 PY	31.37/100 PY	p = 0.505
Luetkemeyer et al. (2023) ¹⁶	200 mg p.e.	52/257 quarterly visits (20.2%), MSM on PrEP	52/570 quarterly visits (9.1%), MSM on PrEP	RR 0.45 (95% CI: 0.32–0.65), p < 0.001
		26/128 quarterly visits (20.3%), MSM with known HIV infection	27/305 quarterly visits (8.9%), MSM with known HIV infection	RR 0.43 (95% CI: 0.26–0.71), p = 0.001
Molina et al. (2023) ¹⁵	200 mg p.e.	41.3/100 PY	20.5/100 PY	aHR 0.49 (95% CI: 0.32–0.76), p = 0.001

Explanation: The table presents data on the effectiveness of antibiotic STI prophylaxis with doxycycline regarding the reduction of the incidence of *Neisseria gonorrhoeae* infections obtained from randomized controlled studies that included men who have sex with men (MSM) and, in part, trans women.

Abbr.: aHR, adjusted Hazard Ratio; HR, Hazard Ratio; p.e., post-expositionem; PY, person-years; RR, Risk Ratio

TABLE 7 Data from randomized controlled trials on the effectiveness of antibiotic STI prevention with doxycycline in reducing the incidence of bacterial STIs (combined outcome; typically syphilis, chlamydia, gonorrhoea).

Study	Mode of intake	Incidence in control group	Incidence in intervention group	Effect estimate
Bolan et al. (2015) ¹⁷	100 mg daily	15/49 visits (30.6%)	6/53 visits (11.3%)	OR 0.30 (95% CI: 0.08–1.09), p = 0.07
Molina et al. (2018) ¹⁴	200 mg p.e.	69.7/100 PY	37.7/100 PY	HR 0.53 (95% CI: 0.33–0.85), p = 0.008
Tattersall et al. (2020), Grennan et al. (2021) ^{18,21} , „DuDHS trial“	100 mg daily	139.8/100 PY	33.9/100 PY	OR 0.18 (95% CI: 0.05–0.68)
Luetkemeyer et al. (2023) ¹⁶	200 mg p.e.	82/257 quarterly visits (31.9%), MSM on PrEP	61/570 quarterly visits (10.7%), MSM on PrEP	RR 0.34 (95% CI: 0.24–0.46), p < 0.001
		39/128 quarterly visits (30.5%), MSM with known HIV infection	36/305 quarterly visits (11.8%), MSM with known HIV infection	RR 0.38 (95% CI: 0.24–0.60), p < 0.001
Molina et al. (2023) ¹⁵	200 mg p.e.	Syphilis, chlamydia: 35.4/100 PY	Syphilis, chlamydia: 5.6/100 PY	Syphilis, chlamydia: aHR 0.16 (95% CI: 0.08–0.30), p < 0.001

Explanation: The table presents data on the effectiveness of antibiotic STI prophylaxis with doxycycline regarding the reduction of the incidence of at least one of the measured bacterial STIs, obtained from randomized controlled studies that included men who have sex with men (MSM) and, in part, trans women. In the study by Molina et al. (2023), only Syphilis and Chlamydia infections were considered.

Abbr.: aHR, adjusted Hazard Ratio; HR, Hazard Ratio; OR, Odds Ratio; p.e., post-expositionem; PY, person-years; RR, Risk Ratio

combined, and the reduction was 84%. In the other studies, the reduction in the incidence of syphilis, Chlamydia trachomatis infections, and gonorrhoea as a combined outcome ranged from 47% to 82%.^{14,16–18}

In two studies conducted in France, there was no impact of post-exposure doxycycline prophylaxis on the incidence of *Mycoplasma (M.) genitalium*.^{15,23}

Regarding quality of life when using antibiotic STI prevention, no data from longitudinal studies were identified. However, cross-sectional studies from the USA, Canada, and Australia showed a general interest in prophylactic doxycycline use among MSM.^{24–26} In a 2020 survey conducted by the German AIDS Federation (Deutsche Aidshilfe, DAH) among PrEP users and people with known HIV infection,

42% of PrEP users and 25% of people with HIV expressed a general interest in STI prevention (Deutsche Aidshilfe, personal communication A. J. Schmidt). A qualitative study from Australia highlighted that antibiotic STI prevention is likely associated with similar concepts as HIV PrEP, such as the idea of having “peace of mind” during sex.²⁷

Benefits of antibiotic STI prevention at the population level

In a modelling study²⁸ various scenarios were examined to quantify the impact of antibiotic STI prevention on the population-based incidence of syphilis. The study used

a closed model with a dynamic cohort of 10,230 sexual minority men in Philadelphia, USA. Over a period of 10 years, assuming that 20% of MSM and other male members of sexual minorities used post-exposure STI prevention with doxycycline with an 80% adherence rate, there would be a moderate decrease in syphilis incidence by 10%.²⁸ It is important to note that the preventive antibiotic intake in the modelling was not stratified by risk behavior; instead, it was applied to all men who belong to sexual minorities.

In another modelling study²⁶ various scenarios were examined. Assuming a 70% effectiveness rate and utilization by 50% of MSM, an 85% reduction in syphilis diagnoses was predicted within a ten-year time frame.

No other studies on the impact of antibiotic prophylaxis with doxycycline on the population-based incidence of syphilis were identified.

Considering the proportion of MSM eligible for HIV PrEP in Germany, which is approximately 7.5%,²⁹ the use of antibiotic STI prophylaxis by 20% or 50% of MSM appears unrealistic.

The significant differences between the modelling studies highlight the uncertainties inherent to modelling studies. From the current point of view, the assumptions of the models (such as the use of STI prophylaxis by at least 20% of MSM or consistent use by a certain proportion of MSM over a period of 10 years) appear unrealistic. However, the modelling studies depict implementation scenarios and their potential effects on syphilis incidence. The results show that antibiotic STI prevention with doxycycline could be a complementary measure to reduce STI incidence, which, depending on its implementation in the target groups, could lead to a moderate to substantial reduction in syphilis in the general population. Theoretical considerations about the epidemiology of syphilis suggest that the dynamics of the syphilis epidemic may be partly dependent on the perpetuation of the infection in a “core group” with high transmission risk.³⁰ Therefore, a behavior-based stratification of implementation appears to be a crucial prerequisite and should be more strongly considered in future modelling studies.

Risks of antibiotic STI prevention at the individual level

To evaluate the risks of antibiotic STI prevention with doxycycline from an individual perspective, data from the aforementioned randomized controlled trials were extracted (Table 8). In addition, a cohort study was used in which 37 participants took post-exposure doxycycline in addition to HIV PrEP.³¹

Due to its overall relatively good tolerability, the anti-inflammatory antibiotic doxycycline is used for a wide range of bacterial and non-bacterial diseases. There are experiences with its longer-term use over weeks to months,

including its use in chronic inflammatory or autoimmune skin conditions.^{4–6}

As evident from the studies on antibiotic prophylaxis with doxycycline listed above, gastrointestinal adverse effects such as nausea, vomiting or diarrhea are among the common adverse drug reactions; rare gastrointestinal adverse effects are esophagitis and esophageal ulcers.^{32–34} The effects of frequent doxycycline intake on the microbiome remain unclear. In one study, there was no increased risk of *Clostridioides difficile* infections associated with doxycycline intake.³⁵

In the context of a study on the treatment of Q fever endocarditis, weight gain was observed with long-term intake of doxycycline and hydroxychloroquine compared to healthy controls.³⁶ However, in the study by Luetkemeyer et al. (2023), there were no significant changes in weight observed under doxycycline intake compared to the controls during the relatively short observation period.¹⁶

Often, photosensitization occurs during doxycycline intake, necessitating protection from UV exposure during the intake period. Intolerance reactions in the form of allergic reactions can occur, but severe reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, or erythema exsudativum multiforme are rare overall.^{33,34} Changes in blood counts as well as liver and kidney damage are also rare; long-term use of doxycycline is recommended to be accompanied by regular blood, liver, and kidney examinations according to the prescribing information/summary of product characteristics.³³

Contraindications for the use of doxycycline include age under 8 years, pregnancy, breastfeeding, body weight below 50 kg, hypersensitivity, and severe liver dysfunction.³³ Due to the increased risk of intracranial hypertension, doxycycline should not be taken concurrently with isotretinoin. Caution should be exercised regarding drug interactions with the following medications: sulfonyleureas, warfarin (Marcumar), cyclosporine, rifampicin, barbiturates, carbamazepine, diphenylhydantoin, and primidone.³³

Risks of antibiotic STI prevention at the population level

From a public health perspective, there are significant concerns regarding the preventive use of doxycycline as a strategy to reduce the incidence of syphilis in key populations. These concerns primarily revolve around the potential for promoting antimicrobial resistance among various bacterial pathogens, not only within the spectrum of sexually transmitted infections but also beyond, including the microbiome bacteria. In line with the principles of rational antibiotic prescribing (Antibiotic Stewardship), there are concerted efforts across healthcare and agriculture sectors to reduce the overall use of antibiotics.

TABLE 8 Data on the safety of antibiotic STI prevention with doxycycline.

Study	Doxycycline mode of intake	Adverse effects
Bolan et al. (2015) ¹⁷	100 mg daily	– 1/15 participants: Discontinuation of doxycycline due to gastroesophageal reflux
Molina et al. (2018) ¹⁴	200 mg p.e.	– 8/116 (7%) participants: Discontinuation of doxycycline intake due to ADR – Statistically significantly more gastrointestinal AE with doxycycline (53% vs. 41%, $p = 0.05$) – No statistically significant differences in terms of: AE in general, severe adverse events, grade 3/4 adverse events, laboratory adverse events
Tattersall et al. (2020) ²¹ , „DuDHS trial“	100 mg daily	– Gastrointestinal AE in 11 out of 26 (42.3%) with doxycycline vs. 4 out of 26 (15.4%) without antibiotic prophylaxis – A total of 6 AE with doxycycline vs. 2 AE without antibiotic prophylaxis
Luetkemeyer et al. (2023) ¹⁶	200 mg p.e.	– Discontinuation due to AE or personal preference: 2% – No severe or grade 4 AE – 1 case of elevated liver enzyme as a grade 2 AE (possible association) – 3 cases of diarrhea as grade 3 AE (possible association) – 2 cases of headache/migraine as grade 3 AE (possible association)
Molina et al. (2023) ¹⁵	200 mg p.e.	– No statistically significant differences in terms of severe AE (7.8% vs. 5.9%) and grade 3 or 4 AE (3.0% vs. 3.5%) – No severe AE – AE occurred in a total of 19 out of 332 participants (5.7%), primarily gastrointestinal AE
Joseph et al. (2020) ³¹	200 mg p.e.	– Vomiting occurred in 1 out of 37 participants (2.7%) after taking two doses within 24 hours

Abbr.: ADR, adverse drug reactions; AE, adverse events

For example, doxycycline has been extensively used in agriculture in Germany (2020: 140.5 tons of tetracyclines); however, the use of tetracyclines in agriculture has been reduced by more than 75% between 2011 and 2020.³⁷

While a high percentage of *T. pallidum* isolates have molecularly confirmed resistance to macrolide antibiotics, there is currently no evidence of a significant proportion of *T. pallidum* showing reduced susceptibility to tetracyclines.³⁸

In the studies by Luetkemeyer et al. (2023)¹⁶ and Molina et al. (2023)¹⁵ the tetracycline susceptibility of *N. gonorrhoeae* isolates from the study population was examined through culture. In the study by Luetkemeyer et al.,¹⁶ at the time of study inclusion, 4/15 (26.7%) of the culturally examined isolates showed resistance to tetracyclines. Over the course of the study, the proportion of tetracycline-resistant *N. gonorrhoeae* isolates in the group receiving post-exposure doxycycline was higher (5/13, 38.5%) than in the group without antibiotic prophylaxis (2/16, 12.5%). In the study by Molina et al. (2023)¹⁵ tetracycline resistance was detected in all culturally examined *N. gonorrhoeae* isolates, both at study inclusion and during the study. In the course of the study, the doxycycline group had a higher proportion of isolates with high MIC values for tetracycline (MIC > 8 mg/l) (7/21, 33.3%) compared to the group without doxycycline (7/37, 18.9%). In a genomic analy-

sis of worldwide *N. gonorrhoeae* isolates, an association between chromosomally encoded tetracycline resistance and reduced susceptibility or resistance to other antimicrobial agents was observed.³⁹ This association was not observed for plasmid-encoded tetracycline resistance.³⁹ The authors of the study conclude that the impact of antibiotic STI prophylaxis with doxycycline on *N. gonorrhoeae* resistance to tetracyclines and other antimicrobial agents depends on whether doxycycline use selects for chromosomal or plasmid-mediated tetracycline resistance.

In a publication²³ regarding the study by Molina et al. (2018)¹⁴ molecular genetic resistance tests were conducted for a portion of the infections detected during the study involving *M. genitalium*. In this relatively small sample of examined findings, no clear trends or differences were observed between the doxycycline and control groups in terms of macrolide, fluoroquinolone, and tetracycline resistances.

In the study by Molina et al. (2023), the proportion of participants with Methicillin-resistant *Staphylococcus (S.) aureus* (MRSA) in the throat swab and with extended spectrum beta-lactamase (ESBL)-carrying *Escherichia (E.) coli* in the anorectal swab was also examined during the follow-up. Over the course of the study, both groups experienced an increase in MRSA detections in the throat (baseline: 1.8% [doxycycline group] vs. 1.2%; month 12: 9.9% vs. 5.1%) and

ESBL-E. coli detections in the anorectum (baseline: 31.4% vs. 32.1%; month 12: 40.0% vs. 35.6%) – however, as indicated in the presentation of the study (CROI 2023, <https://www.croiwebcasts.org/p/2023croi/croi/119>), there were no statistically significant differences between the groups. In the study by Luetkemeyer et al.¹⁶ varying proportions of doxycycline-resistant *S. aureus* isolates were observed during the study, with higher rates in the doxycycline group (month 6: 21.6% vs. 10.3%; month 12: 16.1% vs. 8.3%). In another study¹⁸ a very small number of isolates examined after six months of daily doxycycline intake showed tetracycline-resistant nasopharyngeal *S. aureus* in two out of five cases.

In addition to the prevention of syphilis and other STIs, the prophylactic use of antibiotic treatments is also being discussed for patients with COPD. A Cochrane review on this topic⁴⁰ also examined the effects on microbial resistance. Due to heterogeneous methods, no meta-analysis of the results could be conducted. One study that investigated the prophylactic use of doxycycline reported an increase in the minimum inhibitory concentration (MIC) of isolates obtained from sputum (most commonly *Streptococcus* spp.) by a factor of 3.74 (95% CI: 1.46–9.58, $p = 0.01$).⁴¹

Overall, long-term doxycycline intake appears to have moderate, transient effects on the oral, respiratory, and gastrointestinal flora; however, the data on this issue are limited, primarily due to relatively small study sizes.⁴² Prospective studies have shown varying proportions of tetracycline-resistant normal flora at study inclusion, but higher proportions after doxycycline intake.

When assessing the development of resistance in the aforementioned bacteria, it is important to note that doxycycline is not the antibiotic of choice for the treatment of staphylococci, streptococci, or pneumococci.³³ However, resistance of these bacteria to doxycycline may serve as a marker for the potential promotion of resistant bacteria through the use of doxycycline.

At present, the available data, especially due to the relatively small number of isolates examined in the studies, are not conclusive regarding the potential impact of antibiotic STI prophylaxis on antimicrobial resistance in the general population. From the perspective of *antibiotic stewardship*, it is generally advisable to reduce the prescription of antibiotic agents.

EPIDEMIOLOGY OF SYPHILIS AND POTENTIAL TARGET GROUPS

The number of reported syphilis infections in Germany has increased steadily since 2010, with the exception of 2020 and 2021, when a decrease in reporting is likely due to the corona virus pandemic (Figure 1). In 2022, the incidence level of 2019 was reached again. The vast majority of infections with available information (approximately 80%–85%) were diagnosed in MSM each year. It can be assumed that cases without a specified transmission route are also

roughly equally distributed among MSM. About two-thirds of the infections in MSM were diagnosed in the age groups between 25 and 49 years. MSM thus constitute a central group for syphilis-specific measures for prevention, diagnosis, and treatment in Germany. Such measures should be readily accessible for MSM.

Based on the data on syphilis incidence in Germany and the inclusion criteria of studies demonstrating the efficacy of antibiotic STI prophylaxis, the German STI Society (DSTIG) recommends that the following two criteria should be met as *necessary criteria* for prescribing antibiotic STI prophylaxis (in addition to other additional criteria listed below): (1) MSM or transgender women who have sex with men, and (2) concurrent use or indication for the use of HIV PrEP or confirmed HIV infection.

The dynamics of the syphilis epidemic are likely partially dependent on the persistence of the infection in key populations with a particularly high risk.³⁰ This theoretical consideration is supported by empirical observations, such as a large study involving MSM using PrEP in Australia, where 5.7% of participants accounted for 36.1% of diagnosed STIs.⁴³

From the perspective of DSTIG, it therefore seems reasonable to initially make antibiotic STI prophylaxis – as an effective measure for preventing syphilis infections, the effects of which on the emergence of antimicrobial resistance at the population level are currently unclear – accessible to a limited group of individuals with a particularly high risk of syphilis infections.

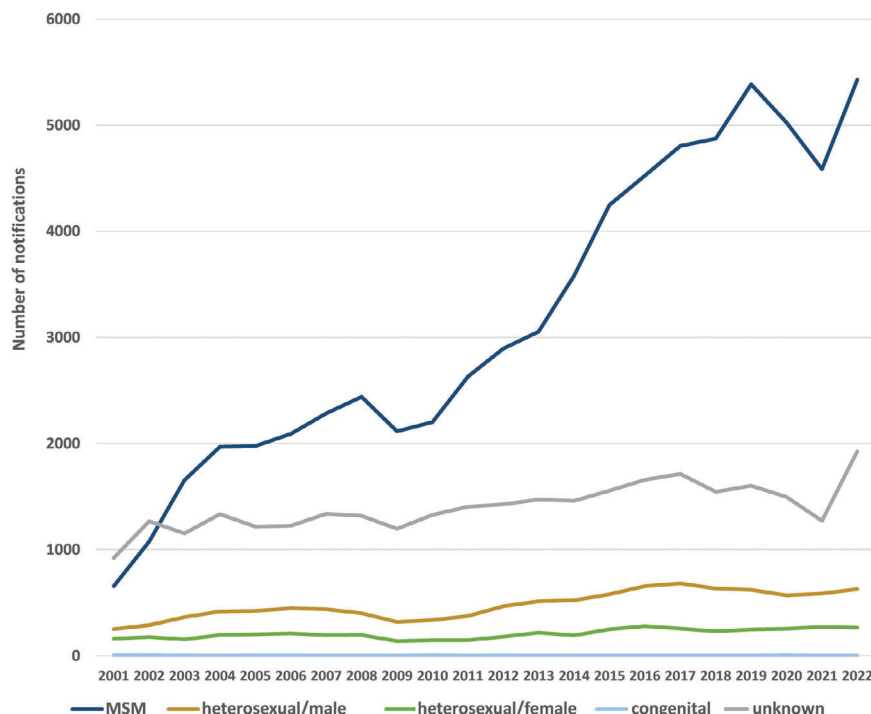
Since conducting a systematic search for risk factors for syphilis infections (within the MSM and transgender women group) would go beyond the scope of this position statement, possible criteria for key populations within the group of MSM and trans women who have sex with men were consensually defined by the group of authors. In addition to the two necessary criteria mentioned above, *at least one additional criterion* should be met for the prescription of antibiotic STI prophylaxis, for example:

- recurrent syphilis infections,
- multiple other (symptomatic) bacterial STIs in the last six months,
- sex with ten or more male partners in the last six months,
- stimulant use during sex (“Chemsex”, e.g., Crystal Meth, GHB/GBL, ketamine, mephedrone),
- group sex.

These risk factors were consensually identified by the author group of the present position statement as being associated with an increased risk of syphilis infections. This list of factors is therefore exemplary and can be supplemented or expanded upon based on a physician’s assessment of individual risk.

Furthermore, from the perspective of the DSTIG, it is unreasonable to define risk events, or occasions for the specific use of antibiotic STI prophylaxis, as any event involving condomless sex, but also to limit the frequency of

FIGURE 1 Syphilis notifications according to the German Federal Protection against Infections Act, Germany, 2001–2022, by Transmission Route (Source: Robert Koch Institute).
Abbr.: MSM, men who have sex with men



antibiotic STI prophylaxis in this regard. To this end, examples of events with an increased risk of syphilis or other STI transmission were also consensually established. These examples include:

- participation in group sex,
- participation in sex-positive parties with multiple sexual partners,
- sex with multiple partners within a short time frame.

Regarding the mentioned risk events or occasions for the use of STI prophylaxis, these are also consensually established examples that can be supplemented or expanded upon based on a physician's assessment of individual risk.

SURVEILLANCE AND RESEARCH

Various aspects of potential long-term consequences of using antibiotic pre- or post-exposure prophylaxis against STIs are currently unclear. Therefore, it is of great importance to accompany this use with suitable surveillance and research activities. The establishment and implementation of broader STI surveillance in Germany is recommended to monitor and analyze the impact of antibiotic pre- or post-exposure prophylaxis against STIs on factors such as the spread of antibiotic resistance determinants and the development of antimicrobial effectiveness within the pathogen population, such as *Treponema pallidum* and *Chlamydia trachomatis* serovars L1–L3. Possible changes in the epidemiological dynamics of conditions like syphilis should be continually monitored. On an individual patient level, possible changes in the microbiome, including considerations

of resistance developments, should be investigated, preferably extending beyond the STI domain to include a broader spectrum of pathogens.

APPROVAL STATUS OF DOXYCYCLINE FOR STI PREVENTION

Doxycycline is not approved for use in terms of STI prevention; therefore, the use of doxycycline to prevent STIs is considered an off-label use. The costs of the prescription are to be borne by the individual concerned, and the legal liability rests with the prescribing physician.

CONFLICT OF INTEREST

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