Deutsche STI-Gesellschaft
Gesellschaft zur Förderung der Sexuellen Gesundheit

Position Statement of the German STI Society
(Deutsche STI Gesellschaft, DSTIG):

Antibiotic STI Prevention with Doxycycline („Doxy-PEP“, „Doxy-PrEP“)

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Content

1. 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 demand and body of evidence for the preventive 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 "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 of 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 insufficient 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, 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 200mg 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 below. 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.**
- **The 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 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 six months for MSM[1], remains crucial to effectively prevent long-term harm among at-risk groups and individuals.**

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)	• Men who have sex with men (MSM) **or** • Trans women who have sex with men
	2)	• Concurrent use or indication for use of HIV PrEP **or** • Known HIV infection
Additional criteria, examples	• 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	• 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. Abbreviations: STI, sexually transmitted infection.

[1] The recommendation for biannual syphilis screening for MSM is based on a syphilis modelling study (Balakrishna et al., 2021, PLoS Comput Biol 17(19): e1009529, DOI: 10.1371/journal.pcbi.1009529) and data from the Swiss STAR Trial (Schmidt et al., 2020, Swiss Medical Weekly 150:w20392, DOI: 10.4414/smw.2020.20392). Australian guidelines recommend syphilis screening every three months for MSM with ten or more partners per year (Templeton et al., 2014, Sexual Health 11, 217-229, DOI: 10.1071/SH14003).

2. 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 (1), rosacea (2), and bullous pemphigoid (3), as well as in Switzerland, France, and the Anglo-American region, for malaria prophylaxis (4).

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* infections (5) and syphilis (6).

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 (7-10). 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 (11).

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, 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.

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	- Reduction of the risk of sexually transmitted infections (STIs), especially syphilis and chlamydia infections - Improved quality of life, less worrisome sex	- Reduction in syphilis incidence - Reduction in the incidence of chlamydia infections
Potential Risks	- Short- and long-term adverse effects - Undesirable immunological effects - Alteration of the gastrointestinal microbiome	- Promotion of antimicrobial resistance in bacterial STIs - Promotion of antimicrobial resistance in bacterial pathogens in general

3. Definitions and clarification of terminology

3.1. Doxy-PEP/-PrEP: Definition and modes 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 3.2).

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 200mg is taken within 24 to a maximum of 72 hours after a risk event (12-14). 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 100mg daily to prevent the acquisition of an STI (15, 16).

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 (12-16). 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 gonorrhoeae* infections (17, 18).

3.2. 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") (6). 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**.

3.3. 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.

4. Benefits and risks of antibiotic STI prevention

As of April 10, 2023, five randomized controlled trials (RCTs) have been published (12-16) on antibiotic STI prevention with doxycycline in MSM, and in some instances, transgender women. An additional study (17, 18) investigated antibiotic STI prevention with doxycycline in cisgender women.

The five RCTs (12-16) in MSM and, in some of these studies, in transgender women who reported having sex with men, comprised a total of 1370 participants. All of these were either concurrently using HIV PrEP or had a confirmed HIV infection. Various additional, 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 the appendix (**Table 8**).

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 and gonorrhoea infections (17, 18). Results from this study are not included in the following sections.

4.1. 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 3**), *Chlamydia trachomatis* infections (**Table 4**), gonorrhoea (**Table 5**), and bacterial STIs as a combined endpoint (

Table 6). 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 (12-16) among participants using preventive doxycycline (**Table 3**), with relatively homogeneous effect estimates. The reduction compared to control groups ranged from 73% to 87% (12-15). In one study, participants with confirmed HIV infection were analysed separately from PrEP-using participants (14), and in one pilot study, only participants with HIV infection were included (15). 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. (15). In one study (16) 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 (12, 13) as well as among PrEP users in the study mentioned above (14), the reduction in syphilis incidence was statistically significant.

The **incidence of *Chlamydia trachomatis* infections** was also significantly reduced in all included studies (12-16) among participants using preventive doxycycline compared with controls (**Table 4**). Likewise, the effect estimates were relatively homogeneous, with the reduction in incidence ranging from 70% to 89% (12-14). In terms of *Chlamydia* infections, the reduction was statistically significant, regardless of whether the study participants were PrEP users or PLWH. In one study (16) 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). All of the aforementioned studies did not differentiate 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 assess the efficacy of preventive doxycycline for these less common serovars.

Table 3: 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) (15)	100mg 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) (12)	200mg 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) (16), „DuDHS trial“	100 mg daily	8,16/100 PY	0/100 PY	*p*=0,98
Luetkemeyer *et al.* (2023) (14)	200mg 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) (13)	200mg p.e.	16,3/100 PY	3,4/100 PY	aHR 0,21 (95%-CI: 0,09 – 0,47), *p*<0,001

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

Table 4: 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) (12)	200mg 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) (16), „DuDHS trial“	100 mg daily	81,63/100 PY	0/100 PY	*p*=0,001
Luetkemeyer *et al.* (2023) (14)	200mg 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) (13)	200mg p.e.	19,3/100 PY	2,1/100 PY	aHR 0,11 (95%-CI: 0,04 – 0,30), *p*<0,001

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

In terms of the **incidence of gonorrhoea**, a reduction was observed in all studies (12-15, 19), but the data were much more heterogeneous compared to the reduction in syphilis and chlamydia incidence (**Table 5**). The reduction in gonorrhoea incidence ranged from 17% to 57% (12-14), and it was statistically significant in only some studies (13, 14). In one study (16), 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 surveillance 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%) (20).

Table 5: 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) (12)	200mg 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) (16), „DuDHS trial“	100 mg daily	57,14/100 PY	31,37/100 PY	*p*=0,505
Luetkemeyer *et al.* (2023) (14)	200mg 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) (13)	200mg p.e.	41,3/100 PY	20,5/100 PY	aHR 0,49 (95%-CI: 0,32 – 0,76), *p*=0,001

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

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 (12-16) (**Table 6**). In the study by Molina et al. (2023) (13), only syphilis and chlamydia infections were 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% (12, 14-16).

Table 6: 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) (15)	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) (12)	200mg 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) (16, 19), „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) (14)	200mg 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) (13)	200mg 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

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

In two studies conducted in France, there was no impact of post-exposure doxycycline prophylaxis on the **incidence of *Mycoplasma genitalium*** (13, 21).

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 (22-24). 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 (11). 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 (25).

4.2. Benefits of antibiotic STI prevention at the population level

In a modelling study (26), 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% (26). It is important to note that the preventive antibiotic intake in the modelling was not stratified by risk behaviour; instead, it was applied to all men who belong to sexual minorities.

In another modelling study (24), 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% (27), 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 ten 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 (28). Therefore, a behaviour-based stratification of implementation appears to be a crucial prerequisite and should be more strongly considered in future modelling studies.

4.3.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 7**). In addition, a cohort study was used in which 37 participants took post-exposure doxycycline in addition to HIV PrEP (29).

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 (1-3).

As evident from the studies on antibiotic prophylaxis with doxycycline listed above, gastrointestinal adverse effects such as nausea, vomiting or diarrhoea are among the common adverse drug reactions; rare gastrointestinal adverse effects are esophagitis and oesophageal ulcers (30-32). The effects of frequent doxycycline intake on the microbiome remain unclear. In one study, there was no increased risk of *Clostridoides difficile* infections associated with doxycycline intake (33).

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 (34). 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 (14).

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 exudativum multiforme* are rare overall (31, 32). Changes in blood counts as well as liver and kidney damage are also

Table 7: Data on the safety of antibiotic STI prevention with doxycycline.

Study	Doxy Mode of Intake	Adverse effects
Bolan *et al*. (2015) (15)	100 mg daily	• 1/15 participants: Discontinuation of doxycycline due to gastroesophageal reflux
Molina *et al*. (2018) (12)	200mg 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: Adverse events in general, severe adverse events, grade 3/4 adverse events, laboratory adverse events
Tattersall *et al*. (2020) (19), „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) (14)	200mg p.e.	• Discontinuation due to adverse events or personal preference: 2% • No severe or grade 4 adverse events • 1 case of elevated liver enzyme as a grade 2 adverse event (possible association) • 3 cases of diarrhoea as grade 3 adverse events (possible association) • 2 cases of headache/migraine as grade 3 adverse events (possible association)
Molina *et al*. (2023) (13)	200mg p.e.	• No statistically significant differences in terms of severe adverse events (7.8% vs. 5.9%) and grade 3 or 4 adverse events (3.0 vs. 3.5%). • No severe adverse events. • Adverse events occurred in a total of 19 out of 332 participants (5.7%), primarily gastrointestinal adverse events.
Joseph *et al*. (2020) (29)	200mg p.e.	• Vomiting occurred in 1 out of 37 participants (2.7%) after taking two doses within 24 hours

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

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 (31).

Contraindications for the use of doxycycline include age under 8 years, pregnancy, breastfeeding, body weight below 50 kg, hypersensitivity, and severe liver dysfunction (31). 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: sulfonylureas, warfarin (Marcumar), cyclosporine, rifampicine, barbiturates, carbamazepine, diphenylhydantoin, and primidone (31).

4.4. 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. 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 (35).

While a high percentage of ***Treponema 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 (36).

In the studies by Luetkemeyer et al. (2023) (14) and Molina et al. (2023) (13), the tetracycline susceptibility of ***N. gonorrhoeae*** **isolates** from the study population was examined through culture. In the study by Luetkemeyer et al. (14), 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) (13), 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 analysis of worldwide *N. gonorrhoeae* isolates, an association between chromosomally encoded tetracycline resistance and reduced susceptibility or resistance to other antimicrobial agents was observed (37). This association was not observed for plasmid-encoded tetracycline resistance (37). 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 publication (21) regarding the study by Molina et al. (2018) (12), 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 *S. aureus* (MRSA)** in the throat swab and with **extended spectrum beta-lactamase (ESBL)-carrying *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. (14), 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 study (16), a very small number of

isolates examined after six months of daily doxycycline intake showed tetracycline-resistant nasopharyngeal S. aureus in 2 out of 5 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 topic (38) 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) (39).

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 (40). 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's important to note that doxycycline is not the antibiotic of choice for the treatment of Staphylococci, Streptococci, or Pneumococci (31). However, resistance of these bacteria to doxycycline may serve as a marker for the potential promotion of resistant bacteria through the use of doxycycline.

As of the current time, 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.

5. Epidemiology of syphilis and potential target groups

The number of reported syphilis infections in Germany has been steadily increasing since 2010, with the exception of the years 2020 and 2021 when there was likely a decrease in reporting 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.

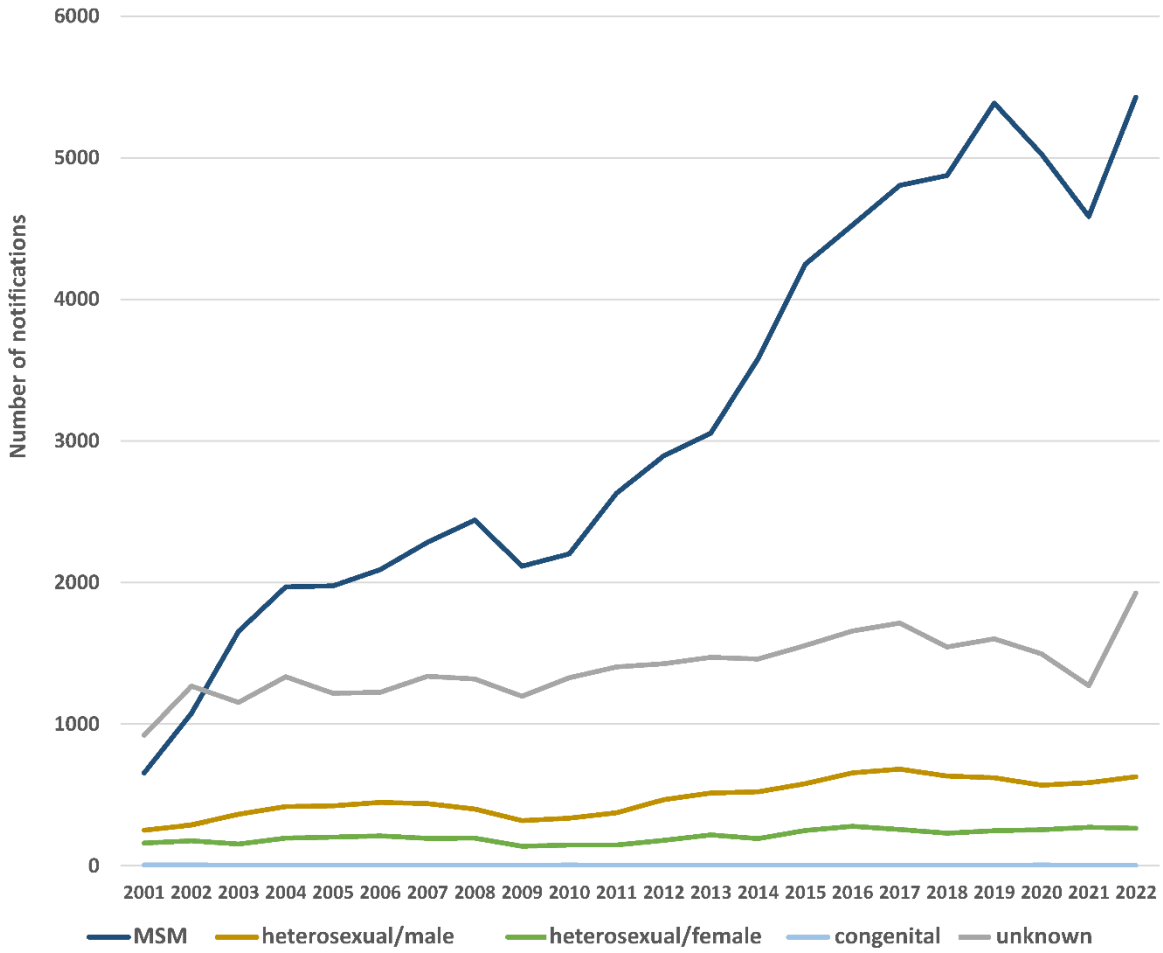

Figure 1: Syphilis notifications according to the Infection Protection Act, Germany, 2001-2022, by transmission route (Source: Robert Koch-Institute, RKI)

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 (28). 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 (41).

From the perspective of DSTIG, it therefore seems reasonable to initially make antibiotic STI prophylaxis, as an effective measure for preventing syphilis infections, whose effects 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 DSTIG, it is not sensible to define **risk events, or occasions for the specific use of antibiotic STI prophylaxis**, solely as any event involving condomless sex but also to limit the frequency of 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.

6. 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 analyse 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.

7. 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.

8. Appendix

8.1. Overview of randomized controlled trials

Table 8: 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) (15)	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	15 participants, intake for 36 weeks, evaluation after 48 weeks	Pilot study, not designed in terms of study size to demonstrate statistically significant differences
			Financial compensation for STI-free status	15 participants, 48 weeks	
Molina *et al*. (2018) (12)	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, Risk event: Unprotected anal or oral sex	Taking doxycycline 200mg within 24 to a maximum of 72 hours after risk events	116 participants, 10 months	
			Control group	116 participants, 10 months	
Grennan *et al*. (2021) (16), Tattersall *et al*. (2020) (19); „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	Continuous intake of doxycycline 100 mg/day	26 participants, 24 weeks	Only conference abstracts available, a pilot study to evaluate feasibility
			Control group	26 participants, 24 weeks	
Luetkemeyer *et al*. (2023) (14)	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	Taking doxycycline 200mg within 72 hours after risk events	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

		chlamydia in the year before study enrolment. Risk event: condomless sex.	Control group	180 participants, 82 PY of follow-up; 120 HIV-PrEP users, 60 with known HIV infection	
Molina *et al*. (2023) (13)	Open-label RCT, 2x2-factorial design (Doxycyclin, Meningococci B vaccination); France	MSM using HIV PrEP with a history of at least one STI in the year before study enrolment. Risk event: Condomless sex.	Taking doxycycline 200mg within 72 hours after risk events	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).	

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

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