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STI-driven antibiotic exposure may shape macrolide and tetracycline resistance in nasal *Staphylococcus aureus* among MSM receiving HIV pre-exposure prophylaxis

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ABSTRACT

Background HIV pre-exposure prophylaxis (PrEP) programmes are associated with intensified sexually transmitted infection (STI) screening and increased incidence of bacterial STIs, resulting in repeated antibiotic exposure. The ecological impact of STI-driven antimicrobial use on resistance in commensal bacteria remains insufficiently characterised, particularly in populations with high antimicrobial exposure such as men who have sex with men (MSM).

Objective To evaluate differences in nasal *Staphylococcus aureus* antimicrobial resistance between MSM receiving PrEP and HIV-negative MSM not on PrEP and to explore behavioural and antibiotic exposure factors associated with resistance.

Methods In this exploratory cross-sectional study, 153 HIV-negative MSM attending an STI clinic in Italy were enrolled (80 PrEP users; 73 controls). Participants underwent nasal swabbing for culture-based isolation and antimicrobial susceptibility testing of *S. aureus*. Antibiotic exposure, behavioural variables and STI history were collected via structured questionnaire.

Results PrEP users reported more sexual partners in the last 6 months (p=0.0009) and higher antibiotic use in the preceding year (p=0.004). Doxycycline postexposure prophylaxis (Doxy-PEP) use was more frequent among PrEP users (16% vs 7%; p=0.08). The cumulative 2-year STI burden was higher in the PrEP group (p<0.0001), driven by *Neisseria gonorrhoeae* infections. *S. aureus* colonisation prevalence did not differ significantly between groups (p=0.17). However, erythromycin (p=0.0008), clindamycin (p=0.004) and tetracycline resistance (p=0.03) were more frequent among PrEP users. Tetracycline exposure was independently associated with tetracycline resistance (p=0.03), whereas PrEP status was not.

Conclusions Among MSM, higher antimicrobial resistance in nasal *S. aureus* may be associated with antibiotic exposure rather than PrEP use per se. These exploratory findings should be interpreted with caution given the limited sample size and lack of detailed exposure quantification but support the need to integrate antimicrobial stewardship into PrEP and Doxy-PEP implementation frameworks. Longitudinal studies are needed to better disentangle the roles of antimicrobial exposure and transmission dynamics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Men who have sex with men (MSM) receiving pre-exposure prophylaxis (PrEP) undergo frequent sexually transmitted infection (STI) screening and repeated antibiotic treatments, and doxycycline-postexposure prophylaxis (Doxy-PEP) use is increasingly implemented in some settings for STI prevention. Recurrent antimicrobial exposure may exert selective pressure not only on target pathogens but also on commensal flora. However, the impact of PrEP-associated antibiotic exposure on resistance in colonising non-target organisms such as *Staphylococcus aureus* remains poorly characterised.

WHAT THIS STUDY ADDS

⇒ In this cross-sectional comparison, nasal *S. aureus* isolates from PrEP users showed higher macrolide, lincosamide and tetracycline resistance compared with non-PrEP controls, despite similar colonisation prevalence. Tetracycline resistance was associated with doxycycline exposure, whereas PrEP status per se was not. Multidrug-resistant isolates were observed only among PrEP users, although numbers were small.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings highlight the need to integrate antimicrobial stewardship into PrEP and Doxy-PEP programmes. Surveillance of resistance in commensal organisms may provide early signals of ecological antimicrobial resistance shifts in high-incidence sexual networks. Further longitudinal and molecular studies are needed to clarify causal pathways and inform prevention strategies.

INTRODUCTION

The widespread implementation of HIV pre-exposure prophylaxis (PrEP) has substantially reduced HIV transmission among men who have sex with men (MSM). However, PrEP programmes are associated with intensified sexually transmitted infection (STI) screening and higher incidence of

bacterial STIs, resulting in repeated antibiotic treatments.[1] In parallel, doxycycline postexposure prophylaxis (Doxy-PEP) is increasingly adopted in some settings for STI prevention.[2]

Repeated exposure to macrolides, tetracyclines and other antimicrobials may exert selective pressure not only on target pathogens but also on commensal microbiota, contributing to the broader antimicrobial resistance (AMR) burden.[3] This phenomenon may promote resistance in colonising organisms that are not directly targeted by treatment.

Staphylococcus aureus is a common coloniser of the anterior nares and serves both as a reservoir for transmission and a potential cause of invasive infections.[4] Changes in its resistance profile may, therefore, have implications beyond the STI setting.

Despite increasing concern regarding cumulative antibiotic exposure in PrEP cohorts, its ecological consequences on resistance in colonising non-target organisms remain poorly quantified.

Data on the impact of repeated STI-related antibiotic exposure on colonising *Staphylococcus aureus* in MSM remain limited.[5] However, recent literature on MSM populations and Doxy-PEP programmes has increased concern regarding off-target AMR in commensal bacteria, including *S. aureus*.[6 7]

Understanding these off-target effects is essential to balance the individual benefits of STI prevention strategies against potential population-level AMR risks. Therefore, we aimed to compare nasal *S. aureus* AMR between MSM receiving PrEP and HIV-negative MSM not on PrEP and to explore behavioural and antibiotic exposure factors associated with resistance.

METHODS

Study design and population

We conducted a monocentric cross-sectional study at the STI Outpatient Clinic (Dermatology Unit) of IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy (September 2025–February 2026). HIV-negative MSM aged ≥18 years attending the clinic for STI screening and counselling were enrolled and categorised into two groups: (1) PrEP users (n=80), defined as individuals with an active PrEP prescription who self-reported current use at the time of enrolment or (2) controls, defined as HIV-negative MSM not on PrEP (n=73). Participants in the PrEP group had been receiving daily PrEP for approximately 16–24 months.

No formal a priori sample size calculation was performed, as this was an exploratory cross-sectional study.

Participants completed a structured questionnaire collecting data on comorbidities, healthcare or livestock exposure, hospitalisation in the previous year, antibiotic use for any reason in the previous 12 months and month preceding enrolment, number of sexual partners in the previous 6 months, enema use, sex toy use, chemsex behaviour and Doxy-PEP use.

Antibiotic exposure, including doxycycline use for both treatment of bacterial STIs and Doxy-PEP, was self-reported and not quantified in terms of dose, duration or cumulative exposure.

History of bacterial STIs during the preceding 2 years was recorded, including genital and extragenital *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection and syphilis.

The 2-year timeframe was selected to capture cumulative behavioural patterns and repeated opportunities for antibiotic exposure over time. This period was considered representative of sustained engagement in STI screening and treatment.

STI episodes were defined as distinct infections by pathogen and anatomical site. Therefore, infections involving different pathogens (eg, *N. gonorrhoeae* and *C. trachomatis*) and/or different anatomical sites (eg, urogenital and extragenital) were counted as separate events. In our clinical setting, STI treatment is generally guided by microbiological diagnosis rather than empirical syndromic management.

Staphylococcus aureus isolation and antimicrobial susceptibility testing

During the clinical visit, participants underwent nasal swabbing (E-swab, Copan, Brescia, Italy) for culture-based isolation and antimicrobial susceptibility testing (AST) of *S. aureus*. Specimens, sent to the Microbiology Unit of the Hospital, were plated onto blood agar and mannitol salt agar (Kima Meus, Padua, Italy) and incubated at 35 °C under aerobic conditions for 48 hours. Suspected *S. aureus* colonies were identified by Matrix-Assisted Laser Desorption/Ionization - Time-Of-Flight Mass Spectrometry (MALDI-TOF MS; Bruker Daltonik GmbH, Bremen, Germany). AST was performed using a commercial broth microdilution method (MicroScan; Beckman Coulter, California). Minimum inhibitory concentrations (MIC) values were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (https://www.eucast.org/, V.16.0). The following antibiotics were tested: erythromycin, clindamycin, tetracycline, oxacillin, levofloxacin, trimethoprim-sulfamethoxazole, teicoplanin, vancomycin. According to EUCAST, tetracycline resistance was defined as MIC>1 mg/L. Inducible clindamycin resistance was assessed using standard phenotypic methods (D-test). Multidrug resistance (MDR) was defined as resistance to ≥3 antimicrobial classes.

Statistical analyses

Categorical variables were compared using Fisher's exact or χ^2 tests. Continuous variables were analysed using Student's t-test or Mann-Whitney U test.

Incidence rate ratios (IRRs) for STI episodes were calculated using Poisson regression, with study group (PrEP vs control) as predictor and the number of participants included as an offset term.

Multivariable analysis of tetracycline resistance was performed using Firth penalised logistic regression to account for sparse data. The model included tetracycline exposure and PrEP status as covariates. Given the limited number of events, no additional variables were included to avoid overfitting. Statistical significance was set at $p<0.05$.

RESULTS

Population characteristics

The two groups (ie, 80 PrEP vs 73 controls) were comparable in age (37.4 vs 36.6 years, p=0.7), healthcare worker status (12.5% vs 13.7%, p=1.00) and chronic comorbidities (30.0% vs 21.9%, p=0.31). However, significant behavioural differences were observed. The PrEP group reported more sexual partners in the previous 6 months (median 15 vs 7, p=0.0009), greater enema use (66.3% vs 42.5%, p=0.003) and higher antibiotic consumption in the preceding year (100% vs 90.4%, p=0.004). Detailed results are presented in table 1.

In the 12 months preceding enrolment, beta-lactams (including benzathine penicillin) were the most frequently reported antibiotics (71.9%), followed by tetracyclines (38.6%) and macrolides (11.8%).

The distribution of antibiotic classes was broadly comparable between PrEP users and controls and did not significantly differ between groups (all p>0.05; see online supplemental table 1).

Table 1 Demographic, behavioural and antibiotic exposure characteristics of the study population

	PrEP group (n=80)	Control group (n=73)	P value
Demographic and behavioural variables			
Age (years; mean±SD)	37.4±11.6	36.6±11.9	0.7
Healthcare worker status	10 (12.5%)	10 (13.7%)	1
Chronic comorbidities	24 (30.0%)	16 (21.9%)	0.3
Antibiotics in the last year	80 (100%)	66 (90.4%)	0.004
Antibiotics in the last month	41 (51.2%)	35 (47.9%)	0.74
Partners in the last 6 months (median; 25%–75% percentile)	15 (5-30)	7 (3-13)	0.0009
Enema use	53 (66.2%)	31 (42.4%)	0.003
Sex toys use	28 (35.0%)	15 (20.5%)	0.05
Chemsex	12 (15.0%)	5 (6.8%)	0.13
Doxy-PEP	13 (16.2%)	5 (6.8%)	0.08
Staphylococcus aureus nasal colonisation	21 (26.2%)	12 (16.4%)	0.17

PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis.

Despite a high prevalence of antibiotic exposure in both populations, the frequency and recurrence of exposure may have differed between groups.

The cumulative 2-year STI burden (including genital and extragenital *C. trachomatis* and *N. gonorrhoeae* infections as well as active or latent syphilis) was higher in the PrEP group than in control (326 vs 191 events; 4.07 vs 2.62 events per patient; IRR 1.56, 95% CI 1.30 to 1.86; p<0.0001), mainly driven by *N. gonorrhoeae* infections (IRR 2.11, 95% CI 1.63 to 2.73; p<0.0001). In contrast, no statistically significant differences were observed for *C. trachomatis* or syphilis infections. Detailed results of STI episodes by pathogen are provided in online supplemental table 2.

Staphylococcus aureus nasal colonisation and AMR

Nasal colonisation was identified in 33 participants (21 PrEP vs 12 controls; 26.2% vs 16.6%; p=0.17). Nasal colonisation was identified in 33 participants (21 PrEP vs 12 controls; 26.2% vs 16.6%; p=0.17). Characteristics of colonised participants according to PrEP status are provided in online supplemental table 3. Among colonised participants, Doxy-PEP use was more frequent in the PrEP group, whereas other behavioural and exposure characteristics showed patterns broadly similar to those observed in the overall cohort

Among colonised individuals, marked differences emerged in resistance profiles, as displayed in table 2. Erythromycin and clindamycin resistance were substantially higher among PrEP users. Among clindamycin-resistant isolates, inducible resistance was observed in 16 out of 17 cases, indicating a predominance of inducible MLS_B resistance. Tetracycline resistance was observed only among PrEP users (p=0.03).

Coresistance to erythromycin and tetracycline was observed in seven isolates. Although erythromycin-resistant strains were more likely to exhibit tetracycline resistance (33.3% vs 8.3%), this association did not reach statistical significance (p=0.206).

Doxy-PEP was associated with tetracycline resistance (62.5% vs 12.0%; p=0.009). Overall, tetracycline exposure (including doxy-PEP and treatment courses in the preceding 12 months) was also associated with tetracycline resistance in nasal *S. aureus* isolates (46.2% vs 10.0%; p=0.035), whereas macrolide use in the preceding 12 months was not associated with erythromycin resistance (p=0.523). In multivariable analysis, tetracycline exposure remained independently associated with tetracycline resistance (adjusted OR 7.58, 95% CI 1.13 to 50.87; p=0.03), whereas PrEP status did not (p=0.07).

S. aureus MDR isolates were detected only among PrEP users (23.8% vs 0%; p=0.13).

Table 2 Nasal *Staphylococcus aureus* colonisation and antimicrobial resistance profiles among colonised participants

Staphylococcus aureus nasal colonisation	PrEP group (n=21)	Control group (n=12)	P value
Resistance			
Erythromycin	18 (85.7%)	3 (25.0%)	0.0008
Clindamycin*	15 (71.4%)	2 (16.7%)	0.004
Tetracycline	8 (38.1%)	0 (0.0%)	0.03
Oxacillin	4 (19.0%)	1 (8.3%)	0.6
Levofloxacin	1 (4.8%)	0 (0.0%)	1
TMP-SMX	0 (0.0%)	0 (0.0%)	1
Vancomycin	0 (0.0%)	0 (0.0%)	1
Teicoplanin	0 (0.0%)	0 (0.0%)	1
MDR *Staphylococcus aureus*	5 (23.8%)	0 (0.0%)	0.13

*Among clindamycin-resistant isolates, inducible resistance was observed in 16 out of 17 cases.
MDR, multidrug resistance; PrEP, pre-exposure prophylaxis.

DISCUSSION

In this cross-sectional study, we observed higher rates of macrolide, lincosamide and tetracycline resistance in nasal *Staphylococcus aureus* isolates from MSM receiving PrEP compared with HIV-negative MSM not on PrEP. While colonisation prevalence did not significantly differ between groups, the resistance profiles of colonising strains appeared distinct, suggesting that antimicrobial exposure and/or transmission dynamics may contribute to the observed differences, although these findings should be interpreted with caution given the limited sample size and cross-sectional design.

Participants in the PrEP group had been receiving daily PrEP for approximately 16–24 months, indicating sustained engagement in care and repeated opportunities for STI diagnosis and treatment over time. In this context, the 2-year timeframe used to assess STI history was aligned with the duration of PrEP use, allowing a proxy evaluation of cumulative exposure to STI-related antibiotic treatments. Although detailed data on antibiotic dose, duration and frequency were not available, this prolonged period likely reflects repeated antimicrobial exposure.

Consistently, PrEP users exhibited a higher cumulative burden of bacterial STIs over the preceding 2 years, largely driven by *Neisseria gonorrhoeae* infections, and consequently experienced greater overall antimicrobial exposure. Although the distribution of antibiotic classes was broadly comparable between groups and did not significantly differ, a high proportion of participants in both groups reported antibiotic exposure. However, the frequency, recurrence and cumulative exposure may have differed, while detailed data on dose, duration and total antibiotic burden were not available, limiting the ability to assess dose–response relationships.

Although microbiome recovery may occur within months after antibiotic exposure,[8] repeated STI episodes over longer periods may reflect sustained patterns of antimicrobial exposure and associated selective pressure on commensal organisms.[9 10]

Tetracycline resistance was observed only in the PrEP group and was strongly associated with doxycycline exposure. Tetracycline exposure in our study included both doxycycline used for treatment of bacterial STIs and doxycycline used as Doxy-PEP. However, the frequency, dose and duration of these exposures were not quantified, limiting the ability to clearly characterise their relative contribution to resistance selection.

In multivariable penalised logistic regression, tetracycline exposure remained independently associated with tetracycline-resistant *S. aureus*, whereas PrEP status itself did not. This suggests that antimicrobial exposure, rather than PrEP use per se, may represent an important contributing factor in shaping resistance phenotypes. In the context of expanding Doxy-PEP implementation, this observation underscores the potential for off-target ecological effects of repeated doxycycline administration on commensal flora.[2 10 11]

In contrast, macrolide and lincosamide resistance was markedly higher among PrEP users but was not significantly associated with documented macrolide use in the preceding 12 months.

In our clinical setting, azithromycin resistance in *Neisseria gonorrhoeae* has been estimated at approximately 20%–25%, consistent with European surveillance data,[12] suggesting substantial macrolide selective pressure within the local MSM population.

Several mechanisms may account for this pattern. First, cumulative antibiotic exposure beyond the 12-month recall window may have contributed to the persistence of macrolide resistance determinants. The high prevalence of inducible clindamycin resistance observed in our study suggests that MLS_B resistance mechanisms, likely mediated by *erm* genes, may play a major role in this setting.[13] These mechanisms can confer cross-resistance between macrolides and lincosamides and may persist over time even in the absence of recent antibiotic exposure.

Second, bystander selection driven by exposure to other antimicrobial classes may facilitate coselection of linked resistance determinants.[14] Third, acquisition and transmission of resistant strains within highly interconnected sexual networks characterised by frequent antimicrobial exposure may contribute to resistance patterns independently of recent individual antibiotic use.[15] The observed, although non-significant, trend towards coresistance between erythromycin and tetracycline supports the possibility of coselection processes, whereby resistance determinants for macrolides (eg, *erm* genes) and tetracyclines (eg, *tet* genes) may be colocated on mobile genetic elements and selected together under antimicrobial pressure.[10 11]

Although not statistically significant, multidrug-resistant *S. aureus* isolates were detected only among PrEP users. This finding may be consistent with cumulative antimicrobial pressure but may also reflect acquisition and transmission of resistant strains within interconnected sexual networks.

Notably, the absence of a significant difference in overall colonisation prevalence suggests that the observed differences may relate more to resistance selection within colonising strains than to major differences in carriage acquisition. However, given the cross-sectional design, we cannot exclude that differences in resistance profiles may partly reflect acquisition or transmission of resistant strains within sexual networks.

In the general population, nasal *S. aureus* colonisation prevalence is typically estimated at approximately 20%–30%, with studies from Italy reporting similar values.[16] Data specifically in MSM populations are limited and heterogeneous, with most studies focusing on selected subgroups or outbreak settings rather than providing generalisable estimates.[5] In our cohort, colonisation prevalence fell within this expected range and did not significantly differ between groups. However, this interpretation should be made with caution, as transmission dynamics within sexual networks may also play an important role.

Our findings should also be interpreted in the context of the limited but growing literature on *S. aureus* in MSM populations and on the ecological effects of doxycycline-based prevention strategies. Earlier work in MSM attending STI clinics suggested that MRSA epidemiology in this population may differ across settings, with low MRSA prevalence reported in Amsterdam despite concerns raised by outbreaks in other MSM networks.[17] More recently, studies in doxy-PEP-eligible populations have shown that *S. aureus* tetracycline non-susceptibility may already be more prevalent than in the general population and may co-occur with resistance to other agents, including clindamycin.[6] In parallel, recent analyses from doxy-PEP cohorts suggest increased expression of tetracycline-resistance determinants in bystander flora, while effects on *S. aureus* colonisation itself appear less consistent.[7] Taken together, these data support the biological plausibility of off-target resistance selection in highly antibiotic-exposed sexual networks, while also indicating that the epidemiology remains setting-specific and incompletely defined.

This study has several limitations. The relatively small number of colonised participants limited statistical precision, particularly for subgroup comparisons and multivariable analyses, and the study was likely underpowered to detect small-to-moderate differences. Antibiotic exposure was self-reported and restricted to a 12-month window. This limits the ability to assess dose–response relationships and to fully characterise cumulative antimicrobial exposure.

In addition, data on STI testing frequency were not available, precluding assessment of whether differences in antibiotic exposure reflected differences in screening intensity, test positivity or both.

Molecular characterisation of isolates was not performed, limiting the ability to assess clonal transmission and resistance mechanisms. Finally, the cross-sectional design does not allow causal inference, and the observed associations should be interpreted as hypothesis-generating.

Despite these limitations, our findings suggest that STI-driven antibiotic exposure in PrEP settings may contribute to shaping resistance patterns in commensal *S. aureus*, while transmission dynamics within sexual networks may also play a role. As doxycycline-based prevention strategies expand, integrating antimicrobial stewardship into sexual health services will be important to balance the benefits of STI prevention with potential ecological impacts on AMR.

Longitudinal and molecular studies are warranted to better disentangle the relative contributions of antimicrobial exposure and transmission dynamics in this setting.

Correction notice This article was updated to CC-BY on 27/07/26

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