**Long-Run Public Health Impact of Doxycycline Post-Exposure Prophylaxis for Syphilis Prevention: A Modelling Study in Singapore**

Sexually transmitted infections (STIs) are among the most prevalent communicable diseases, impacting global health and well-being. Over 30 different pathogens can be transmitted through sexual contact, and individuals may carry multiple infections simultaneously [1]. Many STIs are asymptomatic, allowing infections to spread unknowingly while increasing the risk of severe complications such as cancer, chronic pelvic pain, ectopic pregnancy, and infertility [1]. Syphilis is among one of the most concerning STIs today, particularly among men who have sex with men (MSM), who are estimated to comprise between 0.03% and 6.5% of the male population across various studies [2]. *Treponema pallidum*, the causative agent of syphilis, is primarily transmitted through unprotected vaginal, anal, or oral intercourse, as well as congenital transmission. The infection progresses in stages. The **primary stage** presents as a painless sore (chancre) at the infection site, healing within weeks. The **secondary stage** appears weeks later with a rash, flu-like symptoms, and mucous membrane lesions. The **latent stage** follows, where early latent syphilis (<1 year) remains infectious, while late latent (>1 year) is typically non-infectious. The **tertiary stage** can develop years later, causing severe complications like neurological damage, cardiovascular disease, and organ failure [3]. For men, **primary, secondary, and tertiary stages are symptomatic**, but the **latent stage is asymptomatic** [3], [4]. Moreover, **early stages (primary, secondary, and early latent) are highly contagious**, whereas late-stage (late latent and tertiary) syphilis is **not infectious** but can cause severe complications.

Unlike many bacterial STIs, syphilis progresses through four main stages, each with distinct clinical characteristics. Some stages are **symptomatic**, while others are **asymptomatic**, making detection and treatment challenging. In Singapore, syphilis screening involves **nontreponemal tests**[[1]](#footnote-1) (e.g., Rapid Plasma Reagin (RPR) test, Venereal Disease Research Laboratory (VDRL) test) for initial detection and disease activity monitoring, followed by **treponemal tests**[[2]](#footnote-2)(e.g., Treponema Pallidum Particle Agglutination (TPPA), Fluorescent Treponemal Antibody-Absorption (FTA-ABS), Enzyme Immunoassay (EIA), Chemiluminescent Immunoassay (CIA)) for confirmation [5]. Since treponemal tests (e.g., TPPA, FTA-ABS, EIA) remain positive for life due to a “serological scar,” doctors use nontreponemal tests (e.g., RPR, VDRL) to determine current syphilis infection and disease activity. If both treponemal and nontreponemal tests are positive, it suggests an active or recent syphilis infection. If the treponemal test is positive but the nontreponemal test is negative, it may indicate a past, treated infection rather than an active one. If the nontreponemal test has a high titer (e.g., RPR 1:8), it suggests active infection, while a low titer (e.g., 1:4) may indicate past infection or low disease activity. In unclear cases, patient history, symptoms, risk factors, and follow-up testing help determine whether treatment is needed.

In Singapore, syphilis incidence remained consistently high, fluctuating between 32.5 and 38.1 per 100,000 population from 2004 to 2018 [6], [7]. Even though syphilis incidence showed a decreasing trend during the COVID-19 pandemic, likely due to reduced sexual activity during lockdowns and decreased testing availability [8], evidence suggests that transmission rates may now be exceeding pre-pandemic levels as non-pharmaceutical interventions have been lifted [9]. This underscores the need for proactive intervention strategies to address public health concerns.

Despite the widespread incidence of bacterial STIs, there are currently no vaccines and limited chemoprophylaxis options available for preventing them, especially syphilis [10]. These infections have been rising in the world, disproportionately impacting gay, bisexual, and other men who have sex with men as well as transgender women (TGW) [10]. To address this growing concern, doxycycline [[3]](#footnote-3) post-exposure prophylaxis (doxy-PEP) has recently gained attention as a promising biomedical strategy for STI prevention. While still in the early stages of clinical adoption, it is being integrated into healthcare practices in countries like the US [12]. This approach involves taking a 200 mg dose of immediate-release doxycycline within 72 hours after condomless sex to reduce the risk of bacterial STIs, including syphilis. A 30- to 90-day supply is typically recommended and clinicians should conduct screenings for HIV and syphilis at least every three months for individuals using doxy-PEP [13]. Additionally, CDC advises that MSM and TGW diagnosed with a bacterial STI (e.g., syphilis) within the past 12 months should be informed about doxy-PEP as a post-exposure prophylaxis option to reduce the risk of reinfection [10].

Clinical evidence from five open-label randomized trials in France [14], [15], the USA [16], [17], and Kenya [18] has demonstrated its high efficacy in lowering the incidence of syphilis among MSM and cisgender women. Additionally, the implementation of doxy-PEP guidelines in San Francisco, California, was linked to a decline in reported cases of early syphilis among MSM and transgender women [19]. A retrospective cohort study at Kaiser Permanente Northern California further found that doxy-PEP use was linked to significant reductions in syphilis incidence among HIV pre-exposure prophylaxis (PrEP) users [20]. Ongoing studies in Canada and Australia aim to further evaluate its effectiveness and broader implications [21], [22]. Moreover, a preliminary modelling study indicates that doxy-PEP could have a significant impact on reducing bacterial STI incidence. An analysis of electronic health records estimated that implementing doxy-PEP for individuals with bacterial STIs, particularly those with concurrent or recurrent infections, could substantially lower overall STI rates among gay, bisexual, and other men who have sex with men (GBM), transgender women, and nonbinary individuals assigned male at birth who accessed STI testing at a community health centre in Boston, Massachusetts [23].

International studies have examined the acceptability and usage of doxy-PEP among MSM. In Australia, a survey found that 75.8% of participants viewed doxy-PEP as an acceptable STI prevention strategy, with 7.5% reporting prior antibiotic use for this purpose [24]. By comparison, condoms were considered acceptable by 45.1% of respondents, while STI PrEP was rated acceptable by 54.0% [24]. Similarly, a US study revealed that 84% of participants were interested in trying doxy-PEP, and 13% had used it within the past year [25], [26].

Despite over five decades of doxycycline use without reported resistance in Treponema pallidum [27], [28], concerns remain regarding potential risks. These include theoretical microbiome disruption and the emergence of antimicrobial resistance (AMR) in other common bacterial pathogens, such as Staphylococcus aureus [29], Streptococcus pneumoniae and Haemophilus influenzae [29], *Borrelia burgdorferi* [30]. At an individual level, prolonged doxycycline use may contribute to AMR in these bacteria, while at a population level, widespread use could drive broader resistance trends [19], [21], [22], [31], [32]. While current evidence suggests that doxy-PEP provides overall benefits, its implementation requires careful monitoring for potential risks, including AMR development and microbiome alterations [10], [33]. Additionally, individuals taking daily doxycycline may experience an increased risk of gastrointestinal and dermatological side effects [10], [13]. Moreover, modelling studies indicate that for doxy-PEP or STI pre-exposure prophylaxis (PrEP) to have a meaningful population-level impact, a substantial proportion of men who have sex with men (MSM) would need to use it. The greatest effect would be achieved by targeting subpopulations at higher risk of sexually transmitted infections (STIs) [21], [34], [35]. A study in [23], found that prescribing strategies based on STI history were more effective than those based on HIV status or PrEP use. However, as this study was conducted in a community health centre in Boston, Massachusetts, its findings may not be generalizable to broader populations.

The goal of this study is to ensure that individuals who would benefit most from the intervention have access to it while minimizing potential adverse effects and preventing the emergence of AMR in common bacterial pathogens, particularly among high-risk MSM populations. To date, no comprehensive population-level modelling study has examined the transmission dynamics of syphilis with doxy-PEP as a prevention strategy. In this study, we aim to assess the efficacy of different doxy-PEP strategies, identify optimal prescribing approaches, and evaluate the feasibility of widespread implementation while mitigating associated risks. For the first time in the literature, we will use a transmission compartmental model to analyse these factors in the contexts of Singapore and the UK. Specifically, we will assess the long-term public health impact of various doxy-PEP strategies, including: (1) **Doxycycline on Attendance (DoA)**: provide doxy-PEP to MSM attending sexual health clinics for STI testing and screening, regardless of their diagnosis; (2) **Doxycycline on Diagnosis (DoD)**: offer doxy-PEP to MSM diagnosed with a bacterial STI (e.g., syphilis) at current visit; (3) **Doxycycline According to Risk (DaR)**: target MSM engaging in high-risk behaviours (e.g., more than 5 partners per year, condomless anal sex, methamphetamine use) or those with a history of prior STIs; (4) **Doxycycline Before Entry (DbE)**: offer doxy-PEP to MSM entering high-risk networks, such as those newly active on dating apps, entering sex work, or relocating to high-incidence areas. We evaluate efficacy by comparing the impact of doxy-PEP against no intervention while keeping behavioural parameters constant. Additionally, we analyse how variations in the following factors influence the effectiveness of each strategy: (1) adherence rate, (2) doxy-PEP efficacy, (3) doxycycline intolerance rate, and (4) discontinuation rate due to transitioning to alternative STI prevention methods.

**Remark 1:** There are two additional strategies that are challenging to quantify within a transmission modelling framework. Therefore, we will discuss them separately: (1) **On-Demand Doxycycline (Community-Driven Distribution):** provide MSM with a “take-home” supply of doxycycline to use after condomless sex or known STI exposure through telehealth platforms to enhance accessibility; (2) **Integration with Behavioural Interventions**: combine doxy-PEP with counselling on safer sex practices, PrEP adherence, and harm reduction strategies for substance use.

To evaluate and compare the effectiveness and efficacy of these strategies, we will develop a novel compartmental model specifically designed for this purpose. Our model will include the following groups: (1) MSM who take doxycycline after condomless sex (i.e., **doxy-PEP**); (2) **MSM who do not take doxycycline after condomless sex (i.e., non-doxy-PEP),** including those who rely on alternative STI prevention methods such as condom use, as well as individuals with contraindications, such as those taking medications or supplements that interact with doxycycline, including antacids and stomach ulcer treatments containing bismuth (e.g., Pepto-Bismol) **[36]**; (3) **MSM who take doxycycline after condomless sex but experience reduced effectiveness** due to factors such as alcohol consumption and inconsistent and irregular use (e.g., skipping doses, delayed intake) (i.e., **doxy-inconsistent**); (4) **MSM who cannot take doxycycline due to medical conditions (i.e., doxy-intolerant),** including but not limited to a history of allergic reactions to doxycycline or related medications, kidney or liver dysfunction **[37]**, as well as those who initially take doxycycline but discontinue use due to side effects (e.g., gastrointestinal discomfort, photosensitivity, esophageal irritation) [38].

**Remark 2:** The first compartment (MSM who take doxycycline after condomless sex) also includes MSM who use doxycycline as a prescribed treatment for bacterial infections, such as skin conditions (e.g., acne, rosacea), urinary and respiratory tract infections, eye infections, and chest and dental infections. Additionally, this group encompasses individuals taking doxycycline for disease prevention (e.g., malaria prophylaxis) or off-label/experimental purposes. Given that this subpopulation is challenging to distinguish due to limited data availability, we will incorporate it into the first compartment, regardless of whether doxycycline use is objectively or subjectively intended for STI PEP prevention. It is important to note that doxycycline is primarily used for prevention, while **penicillin remains the first-line treatment for syphilis**. **Primary, secondary, and early latent syphilis** are treated with a **single dose** of **Benzathine Penicillin G (2.4 million units IM)**. **Late latent syphilis** or **latent syphilis of unknown duration** requires **three doses** of **Benzathine Penicillin G (2.4 million units IM, administered once per week for three weeks)**. **Tertiary syphilis**, including **gummatous and cardiovascular syphilis**, follows the same three-dose regimen. However, **neurosyphilis and ocular syphilis** require **IV Aqueous Penicillin G (18–24 million units per day, given every four hours or via continuous infusion for 10–14 days)**.

In our model, doxy-PEP uptake can occur at four key points: before entering the sexually active population () , upon diagnosis of syphilis (), after testing negative () if offered during routine screening (DoS, i.e., providing doxycycline to individuals attending STI clinics for testing but receiving negative results), or through non-STI medical clinics or informal sources () (e.g., obtaining doxycycline from friends or using alternative prescriptions for bacterial infections such as skin conditions [acne, rosacea], urinary and respiratory tract infections, eye infections, chest and dental infections, malaria prophylaxis, or off-label/experimental purposes) [39]. Our model considers three targeted doxy-PEP strategies (i.e., DbE, DoD, DoS), which can be implemented individually or in combination: (1) DbE; (2) DoD; (3) DoA (i.e., DoD + DoS): a combined approach where doxy-PEP is offered both upon STI diagnosis and after testing negative at STI clinics; (4) DaR: a risk-stratified approach where DoD is provided to individuals in the low-activity group, and DoA is offered to those in the high-activity group (this is equivalent to providing DoD to all individuals while restricting DoS to those at higher risk).

Table 1: Model parameters. Transition rate parameters () are presented in an annual basis. “TD” indicates that parameter values are calculated using the corresponding time-dependent equations. The “\*” symbol denotes parameters that are not disease-specific and are derived from studies on gonorrhoea [40]. The “Prior” indicates that parameter values are inferred from the data using Bayesian framework. Assuming all individuals participate in anal sex also participate in oral sex (i.e., anal sex population is a subset of oral sex population) [41].

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| Symbol | Parameter | Values |
|  | Proportion of the MSM population in group *L* | 0.793 |
|  | Proportion of the MSM population in group *H* | 0.207 |
|  | Annual MSM population entrants (at age 15) | 2780 |
|  | Rate of leaving incubation period (*I P*) | Prior: logN(ln(15), 0.5), approximately 10 to 90 days (median of 21 to 25 days) after exposure [42] |
|  | Rate of leaving primary stage (*I S*) | Prior: logN(ln(10), 0.4), 2 to 8 weeks after primary stages [42] |
|  | Rate of leaving secondary stage (*S E*) | Prior: logN(ln(2), 0.4), less than 1 year after exposure [42] |
|  | Rate of leaving early-latent stage (*E L*) | Prior: logN(ln(0.5), 0.4), more than 1 year after exposure [42] |
|  | Probability of leaving late-latent stage (*L T*) | Prior: logN(ln(0.05), 0.7), from 1 to 46 years after exposure [42], [43] |
|  | Rate of seeking treatment due to symptoms (*P/S/T R*) | Prior: logN(ln(200), 0.6), assuming the same behaviour pattern as gonorrhoea, from 0.7 days to 3.93 days after symptoms [40] |
|  | Rate of recovery after treatment (*R U*) | Prior: logN(ln(20), 0.3), 10 to 28 days for treatment [44] |
|  | Probability of death at tertiary stage | Prior: U(0.08, 0.58), 128 out of 399 of untreated tertiary syphilis result in death by the end of 40 years after exposure [45], 8% to 58% with a greater death rate in males [43] |
|  | Mortality rate at tertiary stage | Prior: logN(ln(0.04), 0.4), 10% to 20% (17.1%) of untreated tertiary syphilis result in death by the end of 40 years after exposure [46] |
|  | Years spent in the sexually-active population | 50 |
|  | Force of infection in group (*U I*) | TD |
|  | Annual rate of partner change in group *L* | 1.989 |
|  | Annual rate of partner change in group *H* | 14.866 |
|  | Probability of transmission per partnership | Prior: U(0,1) |
|  | Annual increase in transmission risk behaviour | Prior: U(0,1) |
|  | Level of assortativity in sexual mixing | Prior: U(0,1) |
|  | Infectious population size of MSM in group | TD |
|  | Initial population size of MSM | 139,000 |
|  | Proportion of all partnerships in the population that involve a member of group | TD |
|  | Rate of screening in the absence of symptoms in group (*E/L R*) | TD |
|  | Initial rate of asymptomatic screening in group *H* | \*Prior: U(0,4) |
|  | Annual increase in screening rate | Prior: U(0,1) |
|  | Ratio of screening rate in group *L* vs group *H* | \*Prior: logN(-0.87,0.39) |
|  | Shape parameter of communicable disease surveillance data | Prior: U(0,1) |
|  | Efficacy of doxycycline against infections | 1-100% |
|  | Scaling factor accounting for doxycycline inefficacy due to inconsistent and irregular usage | 1-100% |
|  | Effective rate of adherence for transitioning from a doxy-inconsistent regimen to an adherent doxy-PEP regimen | TD |
|  | Initial rate of adherence for transitioning from a doxy-inconsistent regimen to an adherent doxy-PEP regimen | Prior |
|  | Transition speed from a doxy-inconsistent regimen to an adherent doxy-PEP regimen | Prior |
|  | Effective doxycycline intolerance rate | Prior |
|  | Effective discontinuation rate of doxy-PEP | TD |
|  | Initial discontinuation rate of doxy-PEP | Prior |
|  | Transition speed for discontinuation of doxy-PEP | Prior |
|  | Effective rate of doxycycline acquisition from non-STI medical clinics | Prior |
|  | Probability of uptake of doxycycline before entry into the sexually-active population | 1-100% |
|  | Probability of uptake of doxycycline on diagnosis | 1-100% |
|  | Probability of uptake of doxycycline on screening with negative results in group | 1-100% |

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Figure 1: Model architecture for syphilis transmission. Individuals enter the sexually active population as uninfected (). Upon infection, they progress through an incubation phase () before advancing to the primary (), secondary (), early latent (), late latent (), and tertiary () stages. The primary, secondary, and tertiary stages are symptomatic, prompting individuals to seek treatment and transition to the recovered state (). In contrast, early latent and late latent stages are asymptomatic, with infections typically detected through screening, leading to treatment and recovery (). Individuals in the tertiary stage face a risk of mortality, permanently exiting the compartments. Notably, only the incubation, primary, secondary, and early latent stages are infectious, while the late latent and tertiary stages are non-infectious. All treated infections are considered cured, with individuals returning to the uninfected state. Individuals may exit the sexually active population due to aging at any stage. The model includes separate compartments for individuals with low and high sexual activity levels (), represented by the purple and grey layers in the figure. Both groups share an identical compartmental structure, though, for clarity, only the transitions in and out of the high-activity group (upper layer) are depicted.

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Figure 2: Model architecture for doxy-PEP. For each doxy-PEP stratum , the population is categorized into compartments representing different stages of syphilis infection.

Model of syphilis transmission:

We compared the observed annual number of syphilis diagnoses with those predicted by our model sing Negative-Binomial likelihoods to allow for over-dispersion in the observation process relative to a Poisson distribution. If ∼ NegBinom(, ), with mean and shape parameter , then:

where the shape parameter characterises the level of clustering or heterogeneity in the observation process, and is the Gamma function. Under the negative binomial distribution .

The likelihoods of was:

where

The likelihood of the observation given the modelled trajectories produced by parameter set was calculated as the product of the likelihoods of the data stream in each year t = 2004, …, 2018.

Model of doxy-PEP:

1. For non-doxy-PEP (N):
2. For doxy-inconsistent (X):
3. For doxy-PEP (D):
4. For doxy-intolerant (M):

For shared variables:

For each doxy-PEP stratum and calendar year , the total number of diagnosed cases , the number of primary-stage diagnoses , the number of secondary-stage diagnoses , the number of early-latent-stage diagnoses , the number of late-latent-stage diagnoses , the number of tertiary-stage diagnoses , the number of unaffected patients screened for syphilis , the number of syphilis tests , are as follows:

**Reference:**

[1] “Global and regional STI estimates,” World Health Organization. Accessed: Feb. 08, 2025. [Online]. Available: https://www.who.int/data/gho/data/themes/topics/global-and-regional-sti-estimates

[2] D. E. Mauck *et al.*, “Population-based methods for estimating the number of men who have sex with men: A systematic review,” *Sex Health*, vol. 16, no. 6, pp. 527–538, Nov. 2019, doi: 10.1071/SH18172.

[3] R. W. Peeling, D. Mabey, M. L. Kamb, X.-S. Chen, J. D. Radolf, and A. S. Benzaken, “Syphilis,” *Nat Rev Dis Primers*, vol. 3, no. 1, p. 17073, Oct. 2017, doi: 10.1038/nrdp.2017.73.

[4] M. E. Clement and C. B. Hicks, “Syphilis on the Rise: What Went Wrong?,” *JAMA*, vol. 315, no. 21, p. 2281, Jun. 2016, doi: 10.1001/jama.2016.7073.

[5] “Syphilis | DSC Clinic - Department of STI Control Singapore,” National Skin Centre. Accessed: Feb. 27, 2025. [Online]. Available: https://www.nsc.com.sg/dsc/prevention-education/sexually-transmitted-infection/types-of-STIs/Pages/Syphilis.aspx?utm\_source=chatgpt.com

[6] “The Communicable Disease Surveillance in Singapore 2004,” Ministry of Health. Accessed: Feb. 08, 2025. [Online]. Available: https://www.moh.gov.sg/others/resources-and-statistics/reports-communicable-disease-surveillance-in-singapore-2004/

[7] “The Communicable Diseases Surveillance in Singapore 2018,” Ministry of Health. Accessed: Feb. 08, 2025. [Online]. Available: https://www.moh.gov.sg/others/resources-and-statistics/the-communicable-diseases-surveillance-in-singapore-2018/

[8] “COMMUNICABLE DISEASES SURVEILLANCE IN SINGAPORE 2019-2020,” Ministry of Health. Accessed: Feb. 08, 2025. [Online]. Available: https://www.moh.gov.sg/others/resources-and-statistics/reports-communicable-diseases-surveillance-in-singapore-2019-2020/

[9] K. Sinka, “The global burden of sexually transmitted infections,” *Clin Dermatol*, vol. 42, no. 2, pp. 110–118, 2024, doi: 10.1016/j.clindermatol.2023.12.002.

[10] L. H. Bachmann, “CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024,” *MMWR Recomm Rep*, vol. 73, 2024, doi: 10.15585/mmwr.rr7302a1.

[11] H. Peyriere, A. Makinson, H. Marchandin, and J. Reynes, “Doxycycline in the management of sexually transmitted infections,” *J Antimicrob Chemother*, vol. 73, no. 3, pp. 553–563, Mar. 2018, doi: 10.1093/jac/dkx420.

[12] J. C. Dombrowski *et al.*, “Evidence-Informed Provision of Doxycycline Postexposure Prophylaxis for Prevention of Bacterial Sexually Transmitted Infections,” *Clinical Infectious Diseases*, p. ciae527, Oct. 2024, doi: 10.1093/cid/ciae527.

[13] D. E. DiMarco *et al.*, *Doxycycline Post-Exposure Prophylaxis to Prevent Bacterial Sexually Transmitted Infections*. in New York State Department of Health AIDS Institute Clinical Guidelines. Baltimore (MD): Johns Hopkins University, 2024. Accessed: Feb. 13, 2025. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK597440/

[14] J.-M. Molina *et al.*, “Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial,” *Lancet Infect Dis*, vol. 18, no. 3, pp. 308–317, Mar. 2018, doi: 10.1016/S1473-3099(17)30725-9.

[15] J.-M. Molina *et al.*, “Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2 × 2 factorial design,” *The Lancet Infectious Diseases*, vol. 24, no. 10, pp. 1093–1104, Oct. 2024, doi: 10.1016/S1473-3099(24)00236-6.

[16] R. K. Bolan, M. R. Beymer, R. E. Weiss, R. P. Flynn, A. A. Leibowitz, and J. D. Klausner, “Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study,” *Sex Transm Dis*, vol. 42, no. 2, pp. 98–103, Feb. 2015, doi: 10.1097/OLQ.0000000000000216.

[17] A. F. Luetkemeyer *et al.*, “Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections,” *N Engl J Med*, vol. 388, no. 14, pp. 1296–1306, Apr. 2023, doi: 10.1056/NEJMoa2211934.

[18] J. Stewart *et al.*, “Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women,” *N Engl J Med*, vol. 389, no. 25, pp. 2331–2340, Dec. 2023, doi: 10.1056/NEJMoa2304007.

[19] M. Sankaran *et al.*, “Doxycycline Postexposure Prophylaxis and Sexually Transmitted Infection Trends,” *JAMA Internal Medicine*, Jan. 2025, doi: 10.1001/jamainternmed.2024.7178.

[20] M. W. Traeger *et al.*, “Doxycycline Postexposure Prophylaxis and Bacterial Sexually Transmitted Infections Among Individuals Using HIV Preexposure Prophylaxis,” *JAMA Internal Medicine*, Jan. 2025, doi: 10.1001/jamainternmed.2024.7186.

[21] J. S. Grant *et al.*, “Doxycycline Prophylaxis for Bacterial Sexually Transmitted Infections,” *Clinical Infectious Diseases*, vol. 70, no. 6, pp. 1247–1253, Mar. 2020, doi: 10.1093/cid/ciz866.

[22] A. Hazra *et al.*, “Filling in the Gaps: Updates on Doxycycline Prophylaxis for Bacterial Sexually Transmitted Infections,” *Clinical Infectious Diseases*, p. ciae062, Feb. 2024, doi: 10.1093/cid/ciae062.

[23] M. W. Traeger, K. H. Mayer, D. S. Krakower, S. Gitin, S. M. Jenness, and J. L. Marcus, “Potential Impact of Doxycycline Post-exposure Prophylaxis Prescribing Strategies on Incidence of Bacterial Sexually Transmitted Infections,” *Clinical Infectious Diseases*, p. ciad488, Aug. 2023, doi: 10.1093/cid/ciad488.

[24] M. Holt *et al.*, “Acceptability of Doxycycline Prophylaxis, Prior Antibiotic Use, and Knowledge of Antimicrobial Resistance Among Australian Gay and Bisexual Men and Nonbinary People,” *Sex Transm Dis*, vol. 52, no. 2, pp. 73–80, Feb. 2025, doi: 10.1097/OLQ.0000000000002079.

[25] M. A. Spinelli, H. M. Scott, E. Vittinghoff, A. Y. Liu, K. Coleman, and S. P. Buchbinder, “High Interest in Doxycycline for Sexually Transmitted Infection Postexposure Prophylaxis in a Multicity Survey of Men Who Have Sex With Men Using a Social Networking Application,” *Sex Transm Dis*, vol. 46, no. 4, pp. e32–e34, Apr. 2019, doi: 10.1097/OLQ.0000000000000942.

[26] M. W. Traeger, D. S. Krakower, K. H. Mayer, S. M. Jenness, and J. L. Marcus, “Use of Doxycycline and Other Antibiotics as Bacterial Sexually Transmitted Infection Prophylaxis in a US Sample of Primarily Gay and Bisexual Men,” *Sexually Transmitted Diseases*, vol. 51, no. 12, p. 763, Dec. 2024, doi: 10.1097/OLQ.0000000000002061.

[27] N. Borel, C. Leonard, J. Slade, and R. V. Schoborg, “Chlamydial Antibiotic Resistance and Treatment Failure in Veterinary and Human Medicine,” *Curr Clin Microbiol Rep*, vol. 3, pp. 10–18, 2016, doi: 10.1007/s40588-016-0028-4.

[28] A. Sanchez *et al.*, “Surveillance of Antibiotic Resistance Genes in Treponema Pallidum Subspecies Pallidum from Patients with Early Syphilis in France,” *Acta Derm Venereol*, vol. 100, no. 14, p. adv00221, Jul. 2020, doi: 10.2340/00015555-3589.

[29] A. Forsgren and M. Walder, “Haemophilus influenzae, Pneumococci, group A streptococci and Staphylococcus aureus: sensitivity of outpatient strains to commonly prescribed antibiotics,” *Scand J Infect Dis*, vol. 14, no. 1, pp. 39–43, 1982, doi: 10.3109/inf.1982.14.issue-1.08.

[30] J. R. Caskey *et al.*, “The Functional and Molecular Effects of Doxycycline Treatment on Borrelia burgdorferi Phenotype,” *Front Microbiol*, vol. 10, p. 690, Apr. 2019, doi: 10.3389/fmicb.2019.00690.

[31] V. J. Cornelisse, B. Riley, and N. A. Medland, “Australian consensus statement on doxycycline post-exposure prophylaxis (doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual and other men who have sex with men,” *Medical Journal of Australia*, vol. 220, no. 7, pp. 381–386, 2024, doi: 10.5694/mja2.52258.

[32] E. A. Meyerowitz, R. Liang, D. Bishop, and C. E. Mullis, “Put a little doxy-PEP in your step: Using doxycycline to prevent chlamydia, syphilis, and gonorrhea infections,” *PLOS Pathogens*, vol. 20, no. 9, p. e1012575, Sep. 2024, doi: 10.1371/journal.ppat.1012575.

[33] V. T. Chu *et al.*, “Impact of doxycycline post-exposure prophylaxis for sexually transmitted infections on the gut microbiome and antimicrobial resistome,” *Nat Med*, vol. 31, no. 1, pp. 207–217, Jan. 2025, doi: 10.1038/s41591-024-03274-2.

[34] D. P. Wilson *et al.*, “Chemoprophylaxis is likely to be acceptable and could mitigate syphilis epidemics among populations of gay men,” *Sex Transm Dis*, vol. 38, no. 7, pp. 573–579, Jul. 2011, doi: 10.1097/OLQ.0b013e31820e64fd.

[35] J. Zeggagh *et al.*, “Incidence and risk factors for recurrent sexually transmitted infections among MSM on HIV pre-exposure prophylaxis,” *AIDS*, vol. 36, no. 8, pp. 1129–1134, Jul. 2022, doi: 10.1097/QAD.0000000000003187.

[36] “Taking doxycycline with other medicines and herbal supplements,” National Health Service. Accessed: Feb. 10, 2025. [Online]. Available: https://www.nhs.uk/medicines/doxycycline/taking-doxycycline-with-other-medicines-and-herbal-supplements/

[37] “Who can and cannot take doxycycline,” National Health Service. Accessed: Feb. 10, 2025. [Online]. Available: https://www.nhs.uk/medicines/doxycycline/who-can-and-cannot-take-doxycycline/

[38] M. H. Junejo, J. L. Marcus, and K. A. Katz, “Doxycycline Postexposure Prophylaxis (DoxyPEP) for Bacterial STI Prevention,” *JAMA Dermatology*, vol. 161, no. 1, pp. 7–8, Jan. 2025, doi: 10.1001/jamadermatol.2024.4567.

[39] “About doxycycline,” National Health Service. Accessed: Feb. 20, 2025. [Online]. Available: https://www.nhs.uk/medicines/doxycycline/about-doxycycline/

[40] L. K. Whittles, X. Didelot, and P. J. White, “Public health impact and cost-effectiveness of gonorrhoea vaccination: an integrated transmission-dynamic health-economic modelling analysis,” *The Lancet Infectious Diseases*, vol. 22, no. 7, pp. 1030–1041, Jul. 2022, doi: 10.1016/S1473-3099(21)00744-1.

[41] J. G. Rosenberger *et al.*, “Sexual Behaviors and Situational Characteristics of Most Recent Male-Partnered Sexual Event among Gay and Bisexually Identified Men in the United States,” *The Journal of Sexual Medicine*, vol. 8, no. 11, pp. 3040–3050, 2011, doi: 10.1111/j.1743-6109.2011.02438.x.

[42] M. E. Tudor, A. M. Al Aboud, S. W. Leslie, and W. Gossman, “Syphilis,” in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2025. Accessed: Mar. 10, 2025. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK534780/

[43] M. E. Kent and F. Romanelli, “Reexamining Syphilis: An Update on Epidemiology, Clinical Manifestations, and Management,” *Ann Pharmacother*, vol. 42, no. 2, pp. 226–236, Feb. 2008, doi: 10.1345/aph.1K086.

[44] L. V. STAMM, “Syphilis: antibiotic treatment and resistance,” *Epidemiol Infect*, vol. 143, no. 8, pp. 1567–1574, Jun. 2015, doi: 10.1017/S0950268814002830.

[45] M. J. Tobin, “Fiftieth Anniversary of Uncovering the Tuskegee Syphilis Study: The Story and Timeless Lessons,” *Am J Respir Crit Care Med*, vol. 205, no. 10, pp. 1145–1158, doi: 10.1164/rccm.202201-0136SO.

[46] E. G. Clark and N. Danbolt, “The Oslo study of the natural history of untreated syphilis: An epidemiologic investigation based on a restudy of the Boeck-Bruusgaard material a review and appraisal,” *Journal of Chronic Diseases*, vol. 2, no. 3, pp. 311–344, Sep. 1955, doi: 10.1016/0021-9681(55)90139-9.

1. Nontreponemal tests (screening tests) detect **reagin antibodies** produced in response to syphilis but can also be positive in other conditions. [↑](#footnote-ref-1)
2. Treponemal tests (confirmation tests) detect **antibodies** specific to Treponema pallidum and remain positive for life. [↑](#footnote-ref-2)
3. A second-generation tetracycline with moderate-spectrum activity that is well tolerated and rapidly absorbed following oral administration [11], which has been extensively used for treating acne, preventing malaria, and managing rosacea [10]. [↑](#footnote-ref-3)