nature communications

Article

https://doi.org/10.1038/s41467-026-68561-7

Impact and cost-effectiveness of doxycycline post-exposure prophylaxis in Australian men who have sex with men

Received: 9 January 2025

Accepted: 7 January 2026

Published online: 21 January 2026

Check for updates

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The optimal implementation of doxycycline post-exposure prophylaxis (doxy-PEP) for preventing bacterial sexually transmitted infections (STIs) among Australian men who have sex with men is unclear due to concerns about antimicrobial resistance and cost-effectiveness. We developed an individual-based model, calibrated to Australian national data, to compare five targeted doxy-PEP strategies with a base case from 2025 to 2034, using a multi-criteria ranking framework to evaluate their epidemiological, resistance, and economic outcomes. All evaluated strategies reduced STIs by 13.0% to 47.8% and were cost-saving. However, compared to the high 73.5% baseline projection for high-level tetracycline resistance by 2034, all strategies yielded higher proportions. This proportion was highest (97.4%) when targeting all HIV pre-exposure prophylaxis users, and lowest (81.2%) for the syphilis diagnosis strategy. This syphilis-focused strategy reduced overall STIs by 16.4%, had the highest benefit-cost ratio (9.2), and ranked highest in 9 of 11 evaluation frameworks. Here, we show that doxy-PEP is an effective, cost-saving intervention, with the syphilis diagnosis strategy representing the most recommended approach to optimally balance benefits and risks.

Sexually transmitted infections (STIs) remain a significant global public health issue, disproportionately affecting gay, bisexual, and other men who have sex with men (GBMSM)[1]. In Australia, diagnoses of gonorrhoea, chlamydia, and syphilis are increasing among GBMSM despite ongoing prevention efforts[2]. These infections not only cause immediate health issues but also facilitate the transmission of HIV and contribute to the emergence of antimicrobial resistance (AMR), creating additional challenges for public health interventions[1]. Recognising the urgency of the situation, the World Health Organization (WHO) has set ambitious targets to reduce the incidence of gonorrhoea and syphilis by 90% and chlamydia by 50% by 2030 compared to 2020 levels[3].

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Doxycycline, a tetracycline antibiotic, has been recommended as a potential prophylactic agent to prevent bacterial STIs[4]. Recent studies have explored the use of doxycycline post-exposure prophylaxis (doxy-PEP) among GBMSM and transgender women, demonstrating promising results in preventing chlamydia and syphilis infections, with moderate effectiveness against gonorrhoea infection[5,6]. However, concerns about its potential to increase AMR have limited its recommendation in clinical practice in many countries[7–9]. In Australia, a consensus statement by Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) indicated broad agreement that doxy-PEP should be considered for preventing STIs among GBMSM, particularly among those at higher risk of syphilis and proposed a range of putative criteria for commencing doxy-PEP[9].

While doxy-PEP's preventive benefits are increasingly recognised, understanding how these benefits are offset by potential AMR risks and the relevant economic implications is crucial for informed policymaking[10]. Although previous modelling studies have examined doxy-PEP's impact on single STIs—such as syphilis in British Columbia and gonorrhoea in the United States—they neither considered targeted implementation approaches nor evaluated cost-effectiveness[11,12]. As a result, they offer limited insights into how doxy-PEP might perform when applied strategically across multiple bacterial STIs.

To address this gap, we developed an individual-based stochastic network model to evaluate the population impact and cost-effectiveness of doxy-PEP in preventing three STIs among GBMSM in Australia. By assessing various doxy-PEP implementation targeted strategies and considering the potential risk of AMR, our study provides key evidence to inform guidelines on using doxy-PEP as a public health intervention.

Results

By incorporating demographic dynamics, the simulated population size evolved from an initial 10,000 individuals in 2012 to a projected 12,543 (95% uncertainty interval [UI]: 12,436–12,641) by 2034 (Supplementary Fig. 13). Besides, our model was successfully calibrated to reflect the temporal trends of increasing incidence rates for gonorrhoea, chlamydia, and syphilis, as well as the rising proportions of *Neisseria gonorrhoeae* (NG) isolates exhibiting ceftriaxone decreased susceptibility (Ceftriaxone DS) or high-level tetracycline resistance (HL TetR) (Supplementary Fig. 15). Using this calibrated model, we compared the epidemiological and economic outcomes of a base-case (no doxy-PEP) and five different doxy-PEP implementation strategies from 2025 to 2034 (Table 1).

Epidemiological impact and doxy-PEP utilisation

We illustrate the increasing STI incidence rates in the base case and the reductions observed after implementing doxy-PEP with various strategies (Fig. 1A–D). In the context of the WHO 2030 goals for STI reduction from 2020 levels (red dashed lines in Fig. 1A–C), modelling projects that by 2030, the five evaluated doxy-PEP strategies could reduce chlamydia incidence by 1.8–76.7% and syphilis incidence by 14.0–95.4%, compared with their respective 2020 levels (black dashed lines). Notably, strategies targeting individuals with two STI diagnoses in the past 12 months or all pre-exposure prophylaxis (PrEP)-using GBMSM were projected to achieve the WHO's chlamydia reduction target, with the latter also meeting the syphilis reduction target by 2030. However, while doxy-PEP initially reduced gonorrhoea incidence, projected 2030 levels under all strategies surpassed the 2020 baseline, typically rebounding within two to three years of implementation due to increasing doxycycline resistance; nevertheless, incidence remained below the projected base-case level.

Annual doxy-PEP prescription volumes and population coverage, defined as the proportion of all GBMSM using doxy-PEP, varied substantially across strategies (Fig. 1E and F). Most scenarios showed a peak in prescriptions in the first year of implementation before stabilising. This resulted in projected average annual population coverage levels ranging from a low value of approximately 2.8% (95% UI: 2.5–3.1%) for the strategy targeting individuals with syphilis diagnosis to a high value of 26.1% (95% UI: 26.0–26.3%) for the strategy targeting all PrEP-using attendees.

Cumulatively (Fig. 1G), in the base case, we projected 48,629 (95% UI: 46,781–50,477) total incident STIs between 2025 and 2034, including 19,665 (95% UI: 18,421–20,908) gonorrhoea infections, 22,458 (95% UI: 20,982–23,934) chlamydia infections, and 6506 (95% UI: 5849–7164) syphilis infections. Across the five intervention strategies, the cumulative number of STIs averted ranged from 6323 (95% UI: 6021–6625) for the strategy targeting all HIV-positive attendees to 23,243 (95% UI: 22,042–24,444) for the strategy targeting all PrEP-using attendees, corresponding to overall STI reductions of 13.0 to 47.8% (Fig. 1G and H). Specifically, the strategy targeting individuals with a syphilis diagnosis averted 7979 (95% UI: 7123–8834) infections, a reduction of 16.4%. The epidemiological impacts required a wide range of intervention intensity, from a cumulative 1195 (95% UI: 1075–1317) prescriptions for the syphilis diagnosis strategy to 11,291 (11,281–11,301) prescriptions for the PrEP-using attendees strategy. Consequently, intervention efficiency, measured as infections averted (IA) per prescription, was highest for the syphilis diagnosis strategy

Table 1 | Summary of doxy-PEP scenarios considered

Doxy-PEP scenarios	Eligibility	Number of eligible people	Explanation
(1) Base case (no doxy-PEP)	NA	NA	We assumed nobody using doxy-PEP currently
(2) One syphilis diagnosis	GBMSM diagnosed with syphilis, both through seeking care for symptomatic infection and through attending for screening (testing in the absence of symptoms).	Small	Aligns with the first criteria recommended in the Australian statement[9]
(3) Two STI diagnoses in 6 months	GBMSM diagnosed with one STI (including gonorrhoea, chlamydia, or syphilis) and another diagnosis in the past six months.	Moderate	Adjusted from the second criteria recommended in the Australian statement
(4) Two STI diagnoses in 12 months	GBMSM diagnosed with one STI and another diagnosis in the past twelve months.	Moderate, but larger than scenario (3)	Adjusted from the second criteria in the Australian statement
(5) HIV+ attendees	HIV + GBMSM, attending sexual health clinics—both those seeking care for symptomatic infections and those attending for routine screening. Doxy-PEP is offered irrespective of STI status.	Moderate	Includes HIV+ individuals attending sexual clinics regularly
(6) PrEP-using attendees	PrEP-using GBMSM, attending sexual health clinics—both those seeking care for symptomatic infections and those attending for routine screening. Doxy-PEP is offered irrespective of STI status.	Most inclusive of all strategies considered	Includes PrEP-using individuals attending sexual clinics regularly

GBMSM gay, bisexual, and other men who have sex with men, *Doxy-PEP* doxycycline post-exposure prophylaxis, *STIs* sexually transmitted infections, *PrEP* pre-exposure prophylaxis.

https://doi.org/10.1038/s41467-026-68561-7

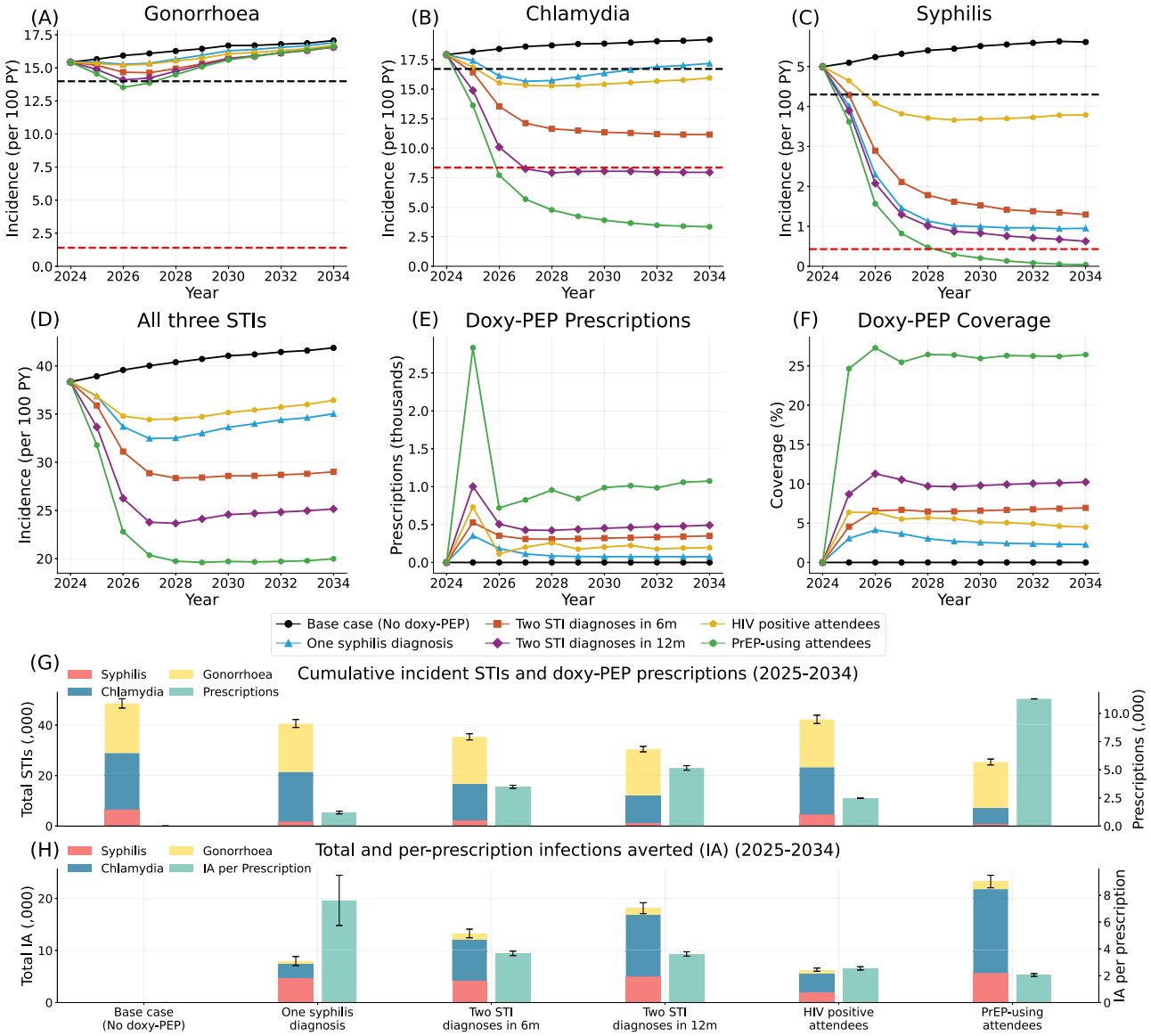

Fig. 1 | Projected impact of various doxy-PEP strategies on STI incidence, doxy-PEP prescriptions, coverage, and intervention efficiency among GBMSM (2024–2034). A–D Illustrate the mean annual incidence rates (per 100 person-years) of gonorrhoea, chlamydia, syphilis, and all three STIs combined, respectively, across different doxy-PEP scenarios. **E** Shows the mean annual doxy-PEP prescriptions (in thousands). **F** Depicts the mean annual doxy-PEP coverage percentage among all GBMSM. **G** Presents the mean cumulative incident STIs (syphilis, chlamydia, gonorrhoea; left y-axis, in thousands) and the mean cumulative doxy-PEP prescriptions (right y-axis, in thousands) over the 2025–2034 period. **H** Displays the mean total infections averted (IA; left y-axis, in thousands) and the mean infections averted per doxy-PEP prescription (IA per prescription; right y-axis) over the 2025–2034 period. All results shown are means (with 95% UI error bars) derived from $n = 900$ independent simulations (30 stochastic simulations for each of the 30 best-fitting parameter sets). The black dashed line in (**A**–**C**) refers to the average incidence rate in 2020. The red dashed lines in (**A**–**C**) represent the 2030 target incidences, derived by reducing respective 2020 incidences to meet WHO's reduction targets (90% for gonorrhoea, 50% for chlamydia, and 90% for syphilis). Doxy-PEP doxycycline post-exposure prophylaxis, GBMSM gay, bisexual, and other men who have sex with men, IA infections averted, PrEP pre-exposure prophylaxis, PY person-years, STIs sexually transmitted infections, WHO World Health Organization.

(7.6 IA per prescription; 95% UI: 5.7–9.5) and lowest for the PrEP-using attendees strategy (2.1 IA per prescription; 95% UI: 1.9–2.2).

Impacts on antimicrobial profiles of gonorrhoea

Although all doxy-PEP strategies reduced overall gonorrhoea incidence, they reshaped the antimicrobial susceptibility patterns of remaining infections (Fig. 2). The annual incidence of strains without HL TetR generally decreased (Fig. 2A, B), while the incidence of strains with HL TetR increased, particularly with broader targeting strategies (Fig. 2C, D). Over the 10-year projection, this resulted in a net cumulative increase in all gonorrhoea infections with HL TetR relative to the base case (12,918; 95% UI: 12,051–13,786), as detailed in the All HL TetR category of Fig. 2E. This increase ranged from 955 additional infections (95% UI: 796–1114) when targeting individuals with a syphilis diagnosis, to 3412 additional infections (95% UI: 3139–3684) when targeting PrEP users. Exploratory analyses found that higher doxy-PEP prescription volume was positively correlated with the cumulative increase in infections with HL TetR ($P < 0.001$; Supplementary Fig. 16).

Compared with the base case (2847; 95% UI: 2373–3321), the cumulative number of gonorrhoea infections with Ceftriaxone DS declined across all intervention scenarios, shown as the "All Ceftriaxone DS" category of Fig. 2E. This decrease ranged from 6 (95% UI: −91–104) when targeting individuals with two STI diagnoses in the past 12 months, to 60 (95% UI: −30–150) when targeting individuals with

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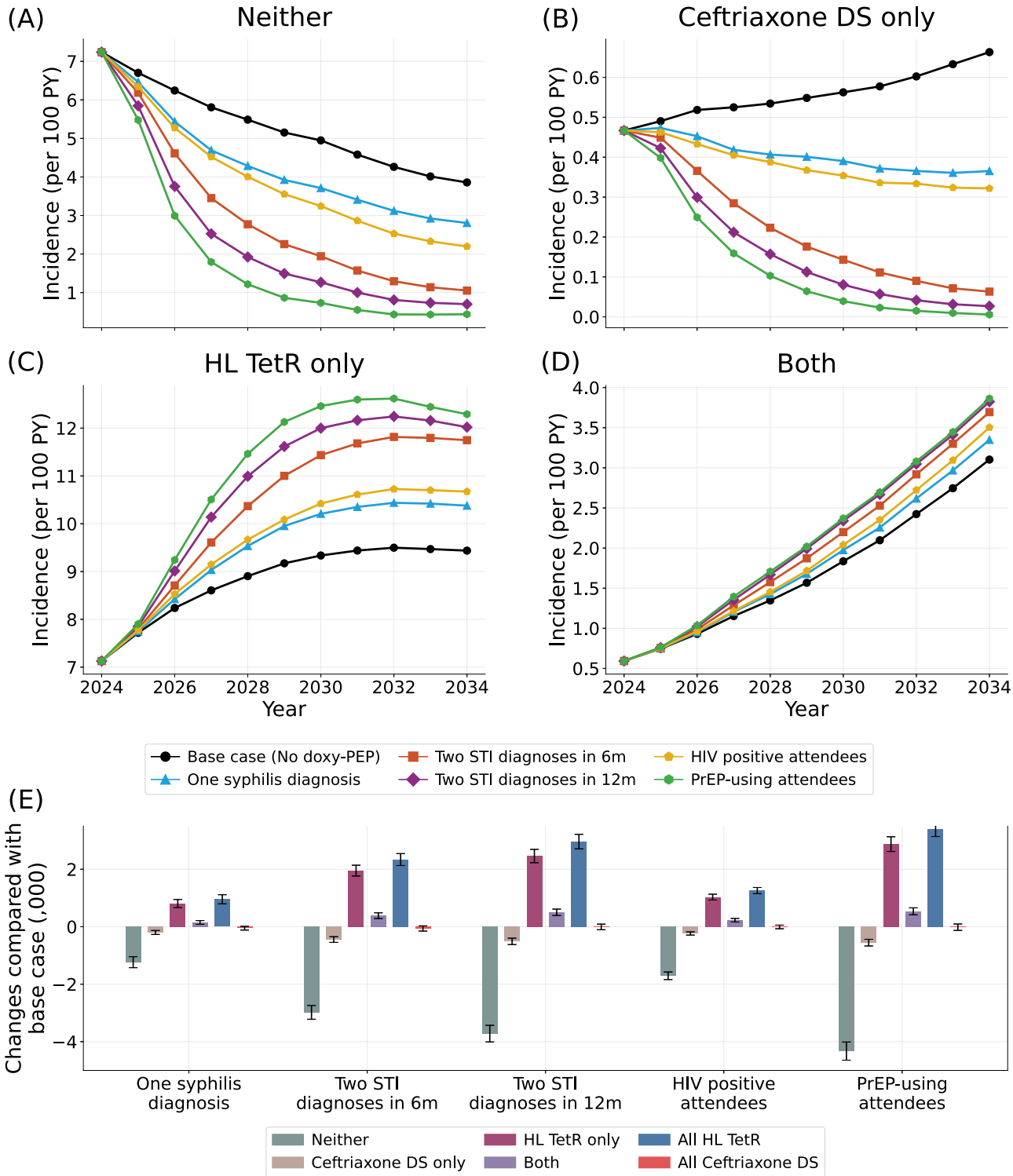

Fig. 2 | Impact of doxy-PEP on incident gonorrhoea infections across different antibiotic susceptibility statuses among GBMSM. Show mean annual gonorrhoea incidence rates (per 100 person-years) under various scenarios, by antibiotic susceptibility status: **A** "Neither" (exhibiting neither Ceftriaxone DS nor HL TetR); **B** "Ceftriaxone DS only"; **C** "HL TetR only"; and **D** "Both" (concurrent Ceftriaxone DS and HL TetR). **E** Projects 10-year (2025–2034) mean cumulative change (with 95% UI error bars) in gonorrhoea infections (thousands) compared to the base case for each intervention scenario. Bars within each scenario are stratified by the four susceptibility statuses (defined in **A**–**D**) and two aggregate categories: "All HL TetR" (sum of "HL TetR only" and "Both") and "All Ceftriaxone DS" (sum of "Ceftriaxone DS only" and "Both"). All results shown are means (with 95% UI error bars) derived from $n = 900$ independent simulations (30 stochastic simulations for each of the 30 best-fitting parameter sets). GBMSM gay, bisexual, and other men who have sex with men, STIs sexually transmitted infections, Doxy-PEP doxycycline post-exposure prophylaxis, PrEP pre-exposure prophylaxis, DS decreased susceptibility, HL TetR high-level tetracycline resistance (used as a proxy for doxycycline resistance).

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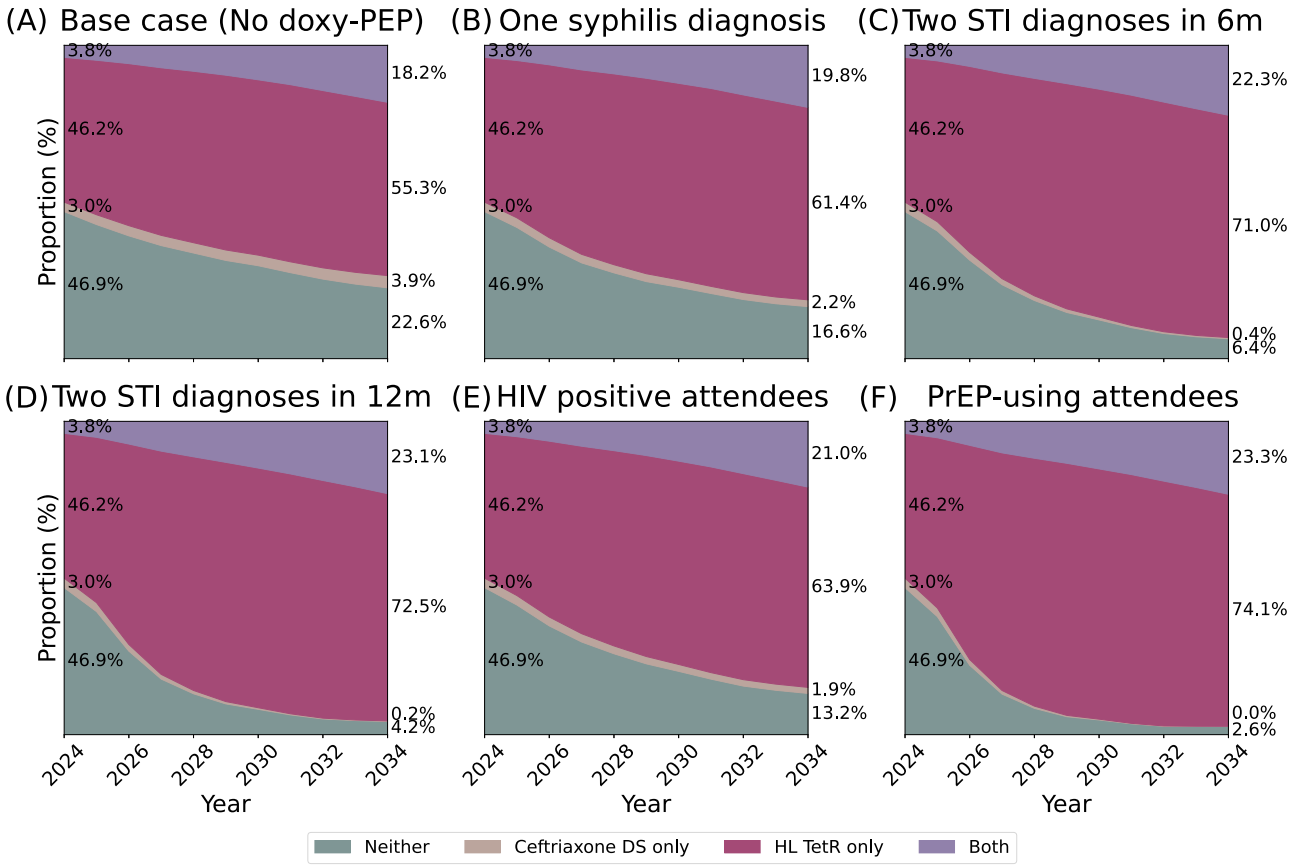

Fig. 3 | Annual proportions of incident gonorrhoea infections with different antibiotic susceptibility statuses across various scenarios, 2024 to 2034. Each (**A**–**F**) corresponds to a specific scenario, illustrating the changing annual proportions of four NG antibiotic susceptibility statuses among incident infections over the period shown. The stacked areas represent infections characterised by: neither Ceftriaxone DS nor HL TetR; Ceftriaxone DS only; HL TetR only; and both Ceftriaxone DS and HL TetR. Percentage labels on the left of each panel denote these respective proportions for 2024 (the year immediately preceding the 10-year intervention period), while labels on the right denote proportions for 2034 (the final year of the 10-year intervention period). All results shown are means derived from $n = 900$ independent simulations (30 stochastic simulations for each of the 30 best-fitting parameter sets). DS decreased susceptibility, HL TetR high-level tetracycline resistance (used as a proxy for doxycycline resistance), Doxy-PEP doxycycline post-exposure prophylaxis, STIs sexually transmitted infections, PrEP pre-exposure prophylaxis.

two STI diagnoses in the past 6 months. The efficiency frontier analysis shows the syphilis-targeting strategy achieved the greatest reduction in Ceftriaxone DS per increase in HL TetR, with a ratio of approximately 18.7 additional HL TetR infections for every one Ceftriaxone DS infection averted along this efficient segment. (Supplementary Fig. 17). Furthermore, the cumulative infections exhibiting both ceftriaxone DS and HL TetR also increased from 2169 (95% UI: 1796–2543) in the base case to a range of 2318 (95% UI: 1924–2713) for the syphilis-targeting strategy to 2706 (95% UI: 2250–3163) for the strategy targeting PrEP users.

These changes in the cumulative infections were reflected in the annual proportions of each susceptibility profile (Fig. 3). In the base case, the proportion of new infections exhibiting any HL TetR was projected to rise from 50.0% in 2024 to 73.5% by 2034. This proportion increased further under all intervention strategies; by 2034, it ranged from 81.2% for the syphilis-targeting strategy to a high of 97.4% when targeting PrEP users. In the base case, the proportion of infections with Ceftriaxone DS was projected to rise from 6.8% in 2024 to 22.1% by 2034, driven by an expansion of the infections exhibiting both Ceftriaxone DS and HL TetR (3.8 to 18.2%). Under the intervention scenarios, this expansion was amplified. By 2034, the proportion of infections exhibiting both Ceftriaxone DS and HL TetR increased to a range of 19.8% (syphilis-targeting strategy) to 23.3% (targeting PrEP users). Correspondingly, the proportion of infections with Ceftriaxone DS also reached higher levels under most interventions, ranging from 22.0% (syphilis-targeting strategy) to 23.3% (targeting all PrEP users) by 2034 for these same strategies.

Economic evaluations

Between 2025 and 2034, the estimated direct medical cost in the base case was $20.7 million (95% UI: $20.5–$20.8 million). All five doxy-PEP strategies reduced these costs, with interventions ranging from $18.7 million (95% UI: $18.6–$18.9 million) for PrEP-using attendees to $20.1 million (95% UI: $19.9–$20.3 million) for HIV-positive attendees (Table 2). Similarly, quality-adjusted life-years (QALYs) lost due to STIs decreased substantially from 373 (95% UI: 339–406) in the base case, with projected losses under the intervention scenarios ranging from 74 (95% UI: 69–80) for the PrEP-using attendees strategy to 274 (95% UI: 248–299) for the HIV-positive attendees strategy.

All evaluated doxy-PEP strategies were projected to be cost-saving, yielding negative incremental cost-effectiveness ratios (ICERs) and benefit-cost ratios (BCRs) consistently greater than 1 (Table 2). However, the economic efficiency of the strategies varied substantially. The strategy targeting individuals with a syphilis diagnosis was the most efficient; it reached lowest cost per IA ($13.9; 95% UI: 13.8–14.0) and yielded the highest BCR of 9.2 (95% UI: 7.1–11.3). In contrast, the strategy targeting all PrEP-using attendees, while averting the most infections overall, was the least efficient by these metrics, reaching the highest cost ($43.8; 95% UI: 43.6-44.2) and resulting in the lowest BCR of 1.9 (95% UI: 1.8–2.0).

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Table 2 | Summary of economic outcomes of different doxy-PEP scenarios among GBMSM

Doxy-PEP scenarios	Direct medical cost (A$, 000)	QALYs lost due to STI	Cost of doxy-PEP (A$, 000)	ICER (A$ per QALYs gained)	New IA per Doxy-PEP prescription	Cost per new IA (A$)	Benefit-cost ratio
Base case (no doxy-PEP)	20,661 (20,475 to 20,846)	373 (339 to 406)	-	-	-	-	-
One syphilis diagnosis	19,726 (19,588 to 19,864)	131 (121 to 140)	111 (100 to 122)	−3405 (−3421 to −3407)	7.6 (5.7 to 9.5)	13.9 (13.8 to 14.0)	9.2 (7.1 to 11.3)
Two STI diagnosis in 6 m	19,463 (19,341 to 19,586)	156 (143 to 169)	311 (299 to 323)	−4093 (−4109 to −4075)	3.7 (3.5 to 3.8)	23.4 (23.5 to 23.7)	3.7 (3.5 to 3.9)
Two STI diagnosis in 12 m	19,097 (18,982 to 19,213)	111 (102 to 120)	463 (445 to 481)	−4201 (−4226 to −4183)	3.6 (3.5 to 3.8)	25.6 (25.5 to 25.8)	3.5 (3.3 to 3.7)
HIV positive attendees	20,093 (19,930 to 20,257)	274 (248 to 299)	225 (225 to 226)	−3451 (−3476 to −3447)	2.6 (2.4 to 2.7)	35.6 (35.3 to 35.8)	2.5 (2.4 to 2.6)
PrEP-using attendees	18,743 (18,618 to 18,868)	74 (69 to 80)	1019 (1018 to 1020)	−3012 (−3049 to −2999)	2.1 (1.9 to 2.2)	43.8 (43.6 to 44.2)	1.9 (1.8 to 2.0)

All results shown are means (with 95% UI) derived from $n = 900$ independent simulations (30 stochastic simulations for each of the 30 best-fitting parameter sets). *GBMSM* gay, bisexual, and other men who have sex with men, *Doxy-PEP* doxycycline post-exposure prophylaxis, *STIs* sexually transmitted infections, *PrEP* pre-exposure prophylaxis, *QALY* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *IA* infections averted, *BCR* benefit-cost ratio.

Multi-criteria evaluation and sensitivity analysis

Our multi-criteria evaluation framework showed that no single strategy was optimal across all eleven policy prioritisations (Fig. 4). The strategy targeting all PrEP-using attendees ranked highest when maximising overall STI and syphilis reduction was the sole priority. Conversely, the strategy targeting individuals with a syphilis diagnosis consistently achieved the highest rankings in frameworks that emphasised minimising the increase in gonorrhoea with HL TetR, maximising the BCR, and all the combined prioritisations frameworks.

To assess the robustness of these findings to parameter uncertainty, extensive one-way sensitivity analyses were performed (Supplementary Figs. 22–25). Varying parameters within their justified ranges did not change the direction of the main outcomes: all strategies consistently reduced overall STIs and syphilis infections while increasing gonorrhoea with HL TetR compared to the base case. However, the BCR could fall below 1 under specific parameter variations.

Across the four key outcome indicators, the condom use frequency among individuals who "sometimes" use condoms was associated with the largest range of uncertainty. Varying this parameter across its range (1 to 99%) substantially altered the projected impacts compared to the initial projections. The reduction in overall STIs ranged from being 99.5% lower (at 99% condom use) up to 168.8% higher (at 1% condom use), and similarly, the reduction in syphilis infections ranged from 99.3% lower (at 99% condom use) up to 190.5% higher (at 1% condom use). Conversely, the increase in gonorrhoea infections with HL TetR was affected in the opposite direction, ranging from being 99.7% lower (at 99% condom use) up to 436.9% higher (at 1% condom use) relative to the initial projection, reflecting the diminished intervention impact at high condom use levels. Critically, increasing the condom use frequency to 99% pushed the BCR below 1 across all evaluated strategies, with the BCR dropping as low as 0.04 (under the strategy targeting PrEP users). Additionally, decreasing the annual number of casual partners for HIV-positive and PrEP-using individuals to 0.5 times the base values also resulted in BCRs below 1 for the strategies targeting HIV-positive attendees and PrEP-using attendees.

Discussion

Based on an individual-based stochastic network model reflecting dynamic population changes for Australian GBMSM, we simulated various doxy-PEP implementation strategies over a ten-year period, revealing important trade-offs between epidemiological impact, AMR, and economic efficiency. Our modelling analysis yielded several key findings. First, all strategies reduced cumulative STI incidence by 13.0 to 47.8% compared to the base case. While broader strategies targeting individuals with two STI diagnoses in 12 months or all PrEP-using attendees met WHO's 2030 chlamydia reduction target (with the latter also meeting the syphilis target), no strategy achieved the gonorrhoea target due to resistance. Second, regarding AMR, the strategy targeting all PrEP-using attendees led to a cumulative increase in gonorrhoea infections with HL TetR approximately ten times the increase observed for the strategy targeting individuals with a syphilis diagnosis. Besides, under the PrEP-using attendees strategy, only 2.6% of new gonorrhoea infections were projected to remain susceptible to doxy-PEP by 2034. Third, all five evaluated strategies were projected to be cost-saving, yielding negative ICERs and BCRs consistently greater than 1. Notably, the syphilis diagnosis strategy was the most economically efficient, demonstrating the highest BCR, the most IA per doxy-PEP prescription, and the lowest cost per infection averted. Fourth, our multi-criteria evaluation framework showed that while the PrEP-using attendees strategy ranked highest for maximising overall STIs and syphilis reduction, the syphilis diagnosis strategy consistently achieved top rankings when minimising HL TetR, maximising BCR, or balancing combined priorities. Finally, sensitivity analyses indicated

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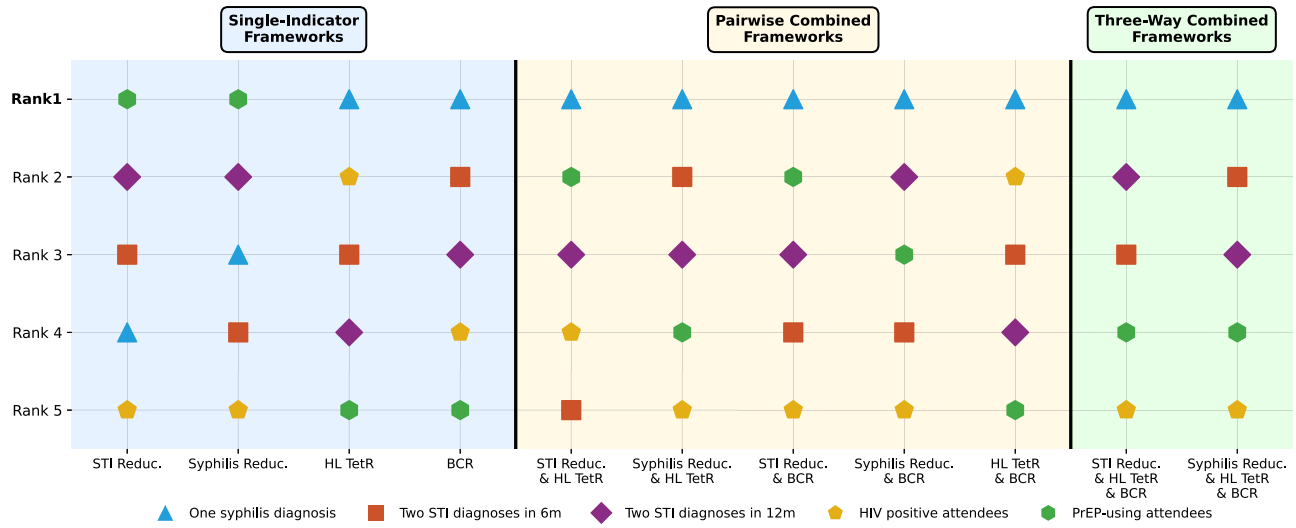

Fig. 4 | Doxy-PEP strategy rankings across different policy prioritisation frameworks. This figure illustrates the relative ranking (from Rank 1 [most favourable] to Rank 5 [least favourable]) of five distinct doxy-PEP implementation strategies across eleven policy prioritisation frameworks. The strategies (defined in the figure legend and detailed in Table 1) were evaluated based on their performance against four key indicators: (1) maximal reduction in overall Sexually Transmitted Infections (STI Reduc.); (2) maximal reduction in syphilis incidence (Syphilis Reduc.); (3) optimal outcomes concerning high-level tetracycline resistance in NG (HL TetR; i.e., minimising its increase); and (4) maximal Benefit-Cost Ratio (BCR). The x-axis specifies each framework, showing rankings based on these indicators considered singly or in combinations. For combined-indicator frameworks, rankings are based on a composite score derived from the sum of min-max normalised indicator values, as detailed in the Methods. Doxy-PEP doxycycline post-exposure prophylaxis, STIs sexually transmitted infections, Reduc. reductions, HL TetR high-level tetracycline resistance, BCR benefit-cost ratio, PrEP pre-exposure prophylaxis.

that the condom use frequency among "sometimes" users was the most influential parameter; higher frequency diminished doxy-PEP's impact on averted infections and, critically, rendered all evaluated strategies no longer cost-saving.

Our model outcomes suggest the strategy targeting individuals diagnosed with syphilis should be strongly considered for prioritisation, a finding that aligns with the Australian consensus statement recommending doxy-PEP primarily for GBMSM at risk of syphilis infection[9]. Our study provides several specific findings to support this recommendation. First, while this strategy achieved a more modest overall STI reduction than broader approaches, it was highly effective and efficient in reducing syphilis incidence by targeting populations likely central to its transmission. Second, the "one syphilis diagnosis" strategy stands out for its relatively favourable AMR profile. It yielded the smallest increase in all gonorrhoea with HL TetR and was the most efficient in trading increased HL TetR for reduced Ceftriaxone DS. However, even this optimal strategy highlighted a substantial trade-off: averting one infection with Ceftriaxone DS was associated with at least 18.7 additional infections with HL TetR, revealing the substantial ecological cost of using doxy-PEP. Third, this strategy demonstrated superior economic efficiency, with the highest BCR, the most IA per prescription, and the lowest cost per infection averted among all strategies. Reflecting these merits, our multi-criteria evaluation framework confirmed that the syphilis diagnosis strategy ranked highest in most prioritisation frameworks. Our findings on the efficiency of syphilis diagnosis-based targeting strategy align with Traeger et al. although their analysis favoured prescribing based on multiple recent STIs rather than syphilis diagnosis alone[13]. Furthermore, their study estimated preventing one STI required over one person-year of doxy-PEP prescription, whereas our dynamic model projects each prescription course averts over two STIs, likely because it captures indirect effects from interrupting transmission chains. Finally, given the severity and cost of syphilis[14], the syphilis-targeting approach still offers significant benefits.

Our findings indicate that introducing doxy-PEP alone may not be sufficient to achieve all the WHO's STI incidence targets among Australian GBMSM. Although broader strategies, such as providing doxy-PEP to all PrEP-using attendees, were projected to meet the WHO targets for both syphilis and chlamydia (while the strategy targeting those with two STI diagnoses in 12 months met the chlamydia target), the PrEP-using attendees strategy also resulted in the largest increase in gonorrhoea with HL TetR. Therefore, it may be more effective to incorporate doxy-PEP into a comprehensive sexual health program that includes other interventions such as vaccination for gonorrhoea and regular screening[11,15,16]. However, decisions regarding screening frequency for doxy-PEP users are complex; while frequent screening for asymptomatic gonorrhoea and chlamydia is generally recommended, it may also lead to increased antibiotic consumption and potentially heighten AMR[17]. A post hoc analysis from the DoxyPEP randomised controlled trial suggested that reducing STI screening for doxy-PEP users could decrease clinic visits but might delay the diagnosis of asymptomatic chlamydia infections[18]. Indeed, the Australian consensus statement underscores the importance of appropriate STI screening for doxy-PEP users[9], and future modelling studies are needed to quantify the population impact of implementing doxy-PEP in conjunction with such potentially enhanced testing protocols, an approach not assessed in the current work.

Despite its benefits in decreasing incident STIs, our study indicates that doxy-PEP may exacerbate the burden of gonorrhoea with HL TetR, affecting its long-term sustainability. The largest cumulative increase in gonorrhoea with HL TetR and a rebound in overall gonorrhoea incidence were observed in broad implementation strategies, such as the one targeting all PrEP-using attendees. This suggests that high-coverage doxy-PEP may rapidly diminish its utility against gonorrhoea, echoing findings from previous modelling studies[12]. Furthermore, while gonorrhoea infections with Ceftriaxone DS only were reduced, those with both Ceftriaxone DS and HL TetR increased, suggesting that doxy-PEP may select for HL TetR in some strains already exhibiting Ceftriaxone DS rather than eliminating them. Crucially, our projections show that the incremental rise in infections exhibiting both Ceftriaxone DS and HL TetR gradually outpaces the reduction in infections with Ceftriaxone DS alone. Since doxy-PEP

confers no protection against strains with such concurrent resistances, their expansion progressively negates the suppression of Ceftriaxone DS, implying that the observed trade-off benefits are strictly limited to the 10-year timeframe. Broader AMR concerns include potential co-selection of ceftriaxone resistance[19,20], and resistance in bystanders like commensal *Neisseria* species[21]. Effective use therefore requires targeted implementation in key populations (such as GBMSM at risk of syphilis)[9], and robust AMR surveillance for pathogens including NG and commensal *Neisseria* species[22]. Ultimately, balancing doxy-PEP's benefits (syphilis/chlamydia) against its diminishing utility for gonorrhoea and wider AMR risks underscores the need for concurrent investment in alternative prevention like vaccines and rapid resistance diagnostics as part of an integrated STI prevention strategy[16,23].

Our one-way sensitivity analyses indicated that varying parameters across their justified ranges did not alter the fundamental findings regarding doxy-PEP's impact: all strategies reduced overall STIs and syphilis while increasing gonorrhoea with HL TetR relative to the base case. Notably, the background condom use frequency among individuals who "sometimes" use condoms emerged as a critical factor influencing the magnitude of these impacts. Our results demonstrated that in simulated settings with higher condom use, the potential infections prevented by doxy-PEP were substantially lower, while the projected increase in gonorrhoea with HL TetR was also mitigated. More importantly, these settings with higher condom use also reduced the BCR below 1 across all evaluated strategies, reaching as low as 0.04 for the strategy targeting PrEP users. Furthermore, in simulated settings with lower sexual activity (decreasing the number of casual partners among HIV-positive and PrEP users), the BCR also fell below 1 for strategies targeting these groups. Together, these findings underscore that impacts and cost-effectiveness projections are highly dependent on the underlying behavioural context and network activity levels. This suggests that deploying doxy-PEP might yield greater net benefits in settings characterised by lower condom use or higher sexual activity, although these conditions could also correspond to larger relative increases in gonorrhoea with HL TetR.

This study has several limitations. First, our model's structure and temporal resolution may not capture all nuances of GBMSM sexual networks and behaviours. For instance, operating on a one-week time step might obscure finer-grained dynamics related to very rapid transmission events or the precise timing of behavioural changes. Furthermore, our model conceptualises sexual acts in a general manner, which precludes modelling of site-specific dynamics like the role of the pharynx in AMR epidemics, and it does not explicitly model the direct impacts of the COVID-19 pandemic on partnership dynamics. However, the model's robust calibration to observed annual STI incidence and AMR trends supports the overall validity of our impact estimations. Second, the modelling of HL TetR development was based on spontaneous probabilities due to the lack of direct data on resistance emergence per doxy-PEP use, which may not fully reflect real-world dynamics. Although our one-way sensitivity analyses did not detect it as most influential indicators, future studies with empirical data on doxy-PEP-induced resistance mutations would enhance model accuracy. Third, due to the lack of available Australian-specific, stage-specific quality-of-life data for these STIs, we applied published lifetime QALY losses per infection to simplify the assessment. Incorporating stage-specific data, should it become available, could yield more precise QALY estimates in future studies. Finally, our model makes certain simplifying assumptions regarding the long-term implementation of doxy-PEP. For instance, we assumed constant uptake and adherence rates over the simulation period. Additionally, by assuming prescriptions occur during routine clinic visits, we did not include costs for separate doxy-PEP-specific appointments or dispensing fees, which may underestimate the true implementation costs.

In conclusion, doxy-PEP can reduce chlamydia and syphilis incidence among GBMSM in Australia and is generally projected to be cost-saving across various implementation strategies. However, its limited impact on gonorrhoea and the potential for increased HL TetR in NG necessitate careful consideration. Targeting individuals diagnosed with syphilis emerges as potentially the most balanced approach when considering STI reduction, BCR, and the change in new gonorrhoea infections with HL TetR.

Methods

Model inputs

We utilised multiple data sources to inform our model parameters. Demographic and behavioural characteristics were derived from published literature and epidemiological datasets, including age distributions, HIV status profiles, PrEP use, annual numbers of casual partners, age-specific sexual activity frequencies, condom use rates, and STI screening intervals (Supplementary Table 1 and Figs. 1–14). In addition, parameters related to the natural history of gonorrhoea, chlamydia, and syphilis (e.g., incubation periods and probabilities of symptomatic infection) were also sourced from existing literature. Parameters such as infection-specific transmission probabilities, initial STI prevalence (stratified by key GBMSM subgroups), and initial AMR levels for NG were estimated through calibration.

Model structure

Drawing on the parameters described above, we developed an individual-based stochastic network model simulating the transmission, progression, and treatment of gonorrhoea, chlamydia, and syphilis among GBMSM in Australia. The model features an evolving sexual partnership network formed by an initial population of 10,000 individuals, which is subject to demographic flows including sexual maturation, immigration, aging out, mortality, and emigration. Each individual was assigned demographic and behavioural attributes, which influenced partnership formation, sexual contact, and infection transmission.

At each model cycle, which was set to a one-week step to balance computational efficiency and accurately capture disease progression, we updated the sexual network by forming and dissolving both regular and casual partnerships. The formation of regular partnerships depended on HIV serostatus-based mixing (Supplementary Fig. 4), while casual partnerships were determined by each individual's annual number of casual partners. STI transmission was then simulated based on scheduled sexual acts within these partnerships. Upon exposure to a partner with an STI, the transmission risk is determined by the number of sexual acts, infection-specific transmission probabilities, and condom use. Further, disease progression and treatment were modelled according to susceptible-exposed-infectious-recovered (SEIR) frameworks tailored to each STI's natural history (detailed model structures are shown in Supplementary Figs. 8–10). Infections can be diagnosed and treated either during symptomatic clinical visits or through asymptomatic screening.

For gonorrhoea infections, we considered four antimicrobial susceptibility states: (1) infections susceptible to both ceftriaxone and doxycycline (i.e., exhibiting neither Ceftriaxone DS nor HL TetR), (2) infections with Ceftriaxone DS; defined as ceftriaxone minimum inhibitory concentration [MIC] > 0.06 mg/L) only, (3) infections with HL TetR; defined as tetracycline MIC > 8 mg/L, used as a proxy for doxycycline resistance) only, and (4) infections with both Ceftriaxone DS and HL TetR[12]. Each transmitted gonorrhoea strain retained its antimicrobial susceptibility profile. Ceftriaxone DS could develop during antimicrobial treatment, while a probability of spontaneous HL TetR development was included in each cycle to account for potential bystander effects contributing to rising resistance levels (independent of the influence of doxy-PEP)[24,25].

Model calibration

We calibrated the model and estimated uncertain parameters (particularly infection-specific transmission probabilities) against the following epidemiological data: (1) annual STI incidence rates and (2) annual STI test positivity rates among GBMSM (2012-2022) from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) system[26], and (3) annual proportions of NG isolates showing Ceftriaxone DS (MIC > 0.06 mg/L) or HL-TetR (MIC > 8 mg/L) from Melbourne Sexual Health Centre (2015–2022).

Using Latin Hypercube Sampling, we generated 10,000 unique parameter sets by drawing values from predefined ranges (Supplementary Table 2). Each set was run 30 times to ensure a robust performance evaluation, and the 30 sets minimising the mean-squared differences between model outputs and calibration targets were selected for all subsequent analyses[27,28]. From these selected sets, key uncertain parameters were estimated; for example, the treatment failure rate for gonorrhoea infections with decreased ceftriaxone susceptibility was calibrated to 8.0% (95% UI: 6.2%–9.8%). All model outputs are reported as the mean and 95% UI from simulations using these 30 selected sets, each run 30 times. Further details on all parameter values and model structure are available in the Supplementary Material.

Intervention scenarios and simulation

We simulated the introduction of doxy-PEP in 2025 and assessed its population impact over ten years until the end of 2034. Six scenarios (Table 1) were considered: a base case without doxy-PEP (scenario 1) and five doxy-PEP implementation strategies (scenarios 2–6) based on potential eligibility options proposed according to the current Australian consensus statement[9]. Scenario 2 focuses on GBMSM with syphilis diagnosis, while scenarios 3 and 4 target GBMSM with two STIs' diagnoses within the past six and twelve months, respectively. Scenario 5 targets all HIV-positive GBMSM and scenario 6 targets all PrEP-using GBMSM; for these two strategies, doxy-PEP is offered when eligible individuals seek care for symptomatic infections or attend for routine screening, which occurs, on average, at least annually for these populations. For all five intervention strategies, we applied initial settings that included an uptake of doxy-PEP at 75%, based on previous acceptability data[29], an adherence rate of 80% for using doxy-PEP within 72 hours of condomless sexual intercourse[4], and a recommended prescription duration of six months[9].

The model incorporated two key mechanisms of doxy-PEP: prevention of STI transmission and the potential impact on AMR, specifically HL TetR in *N. gonorrhoeae*. For prevention, when a participant engaged in condomless sex and used doxy-PEP within 72 h, the probability of establishing an infection was reduced by 45% for gonorrhoea without HL TetR, 81% for chlamydia, and 77% for syphilis, based on pathogen-specific prevention efficacies from a meta-analysis[30]. To model AMR, we simulated the development of HL TetR due to doxy-PEP use in individuals infected with NG strains that initially lacked HL TetR. Specifically, each time an individual with gonorrhoea infections that did not initially exhibit HL TetR used doxy-PEP, there was a probability that the infection would acquire this resistance. Since direct data on the probability of HL TetR emergence per doxy-PEP use is unavailable, we applied the weekly probability of spontaneous HL TetR development in gonorrhoea infections—derived without doxy-PEP use—from our model calibration. Doxy-PEP was considered ineffective against gonorrhoea strains already exhibiting HL TetR.

Impact and economic evaluation of doxy-PEP

We assessed the impact of doxy-PEP on STI incidence and its economic implications over a ten-year period (2025–2034) for the intervention scenarios. The epidemiological impact was evaluated by calculating annual incidence rates and cumulative incident infections of gonorrhoea, chlamydia, and syphilis within the simulated population. These incidence rates were compared with the WHO's targets of reducing the incidence of gonorrhoea and syphilis by 90% and chlamydia by 50% by 2030 relative to 2020 levels[3]. For gonorrhoea, new infections were further stratified by their antibiotic susceptibility profiles to monitor potential changes in resistance patterns.

The economic evaluation was conducted from the perspective of healthcare costs, focusing on direct medical costs associated with screening, diagnosis, and treatment of STIs, based on items specified in the Australian STI guidelines[31]. Intervention costs were calculated as the cost of doxycycline prescribed during clinic visits. The six-month of doxy-PEP prescription duration was assumed to provide 52 administration events (200 mg doxycycline each), a quantity calculated based on a potential usage of up to two such events weekly[4,8,18]. Modelled as event-driven (post-condomless exposure) and adherence-dependent, an individual's course of doxy-PEP concluded once their prescribed doxycycline was exhausted, with re-prescription possible if eligibility criteria were subsequently met. Costs were estimated using the year 2024 prices from the Medicare Benefits Schedule and the Pharmaceutical Benefits Scheme, adjusted to 2025 values using a 3% inflation rate[32,33]. QALYs lost due to STIs were calculated using published estimates of lifetime QALY losses per new infection[34,35]. All costs are expressed in Australian Dollars (AUD), and a discount rate of 3% was applied.

For each intervention scenario, we calculated the differences compared to the base case in cumulative numbers of incident STIs, cumulative numbers of incident gonorrhoea infections with HL TetR, total direct medical costs, intervention costs, and QALYs lost due to STIs between 2025 and 2034. We then determined ICERs for each scenario by comparing costs and QALYs with the base case. Additionally, we calculated IA per doxy-PEP prescription, cost per IA, and BCRs.

Evaluation framework of doxy-PEP strategies

To systematically compare and rank the five doxy-PEP strategies, we used a multi-criteria evaluation framework, assessing performance over 10 years (2025–2034) against four key indicators: two for infection reduction—(1) reductions in overall STIs and (2) reductions in syphilis infection (highlighted due to its prioritisation in the Australian consensus statement); one for AMR—(3) increased gonorrhoea infections with HL TetR, aiming to minimise this; and one for economic efficiency—(4) the BCR, aiming to maximise this.

Strategies were ranked under eleven policy prioritisation frameworks, considering these four indicators singly or in pairwise/three-way combinations (with each combination including at most one of the two infection reduction indicators). For single-indicator frameworks, strategies were ranked directly based on their mean outcome values (1 = most to 5 = least favourable). For frameworks combining multiple indicators, we first normalised the mean outcome values for each indicator to a common [0, 1] scale using min-max normalisation (calculated as [value - minimum value]/[maximum value - minimum value] across all strategies for a given indicator). This normalisation allows comparison and combination of indicators measured on different scales. The adverse indicator, HL TetR increase, was reverse-scaled (using 1 - normalised value) to ensure a higher score is consistently more favourable. A composite score for each strategy was then calculated by summing the normalised values of the constituent indicators, assuming equal weighting. Based on these composite scores, strategies were subsequently ranked, with a higher composite score indicating better overall performance. These rankings (Fig. 4) aid decision-making by showing how strategy prioritisation varies with policy goals.

Sensitivity analysis

One-way sensitivity analyses were conducted for all five doxy-PEP strategies to explore the impact of variations in key model parameters

on projected outcomes, including overall STI reduction, syphilis reduction, change in gonorrhoea infections with HL TetR, and BCRs. A comprehensive range of parameters was varied, encompassing those related to doxy-PEP implementation (such as prescription duration, uptake rates, adherence levels, and pathogen-specific efficacies), STI natural history and epidemiology (including the proportion of symptomatic gonorrhoea infections and probabilities of HL TetR resistance per doxy-PEP use), sexual behaviour (such as condom use patterns among different user groups), and discount rates. These analyses aimed to identify the most influential parameters affecting the outcomes for each strategy (see Supplementary section 5.2 for a full list of varied parameters and their specific ranges). All modelling procedures and analyses were conducted using Python (version 3.12.3). The Supplementary Materials provide full details of the model simulations and assumptions. The code for the version of the model used to perform the analyses is publicly available[36].

Inclusion and ethics statement

This research represents an equitable collaboration between institutions in Australia and China. Researchers from all collaborating institutions contributed substantially to the conception, design, data interpretation, and critical revision of the manuscript. Authorship was determined based on significant intellectual contribution and mutual agreement among all authors. The study focuses on a key population in Australia, and its parameters were informed by data generated within that country to ensure local relevance.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All data used for calibration and conducting model simulation have been included in the Supplementary.

Code availability

The code of modelling and visualising to reproduce all the tables and figures in the main text and Supplementary Information are publicly available on GitHub at https://github.com/Leo-HaoL/Doxy_PEP_Model_AU and permanently archived in Zenodo (DOI: 10.5281/zenodo.17907512).

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Acknowledgements

L.Z. is supported by the Ministry of Science and Technology of the People's Republic of China (2022YFC2304900, 2022YFC2304905), the National Key R&D Program of China (2022YFC2505100, 2022YFC2505103). M.S. is supported by the National Natural Science Foundation of China (Grant number: 12171387), the National Key R&D Program of China (2022YFC2505100) and the Young Elite Professional of the Shaanxi Three Qin Talents Special Support Program (2024STZZK08). J.J.O. is supported by an Australian NHMRC Emerging Leadership Grant (GNT1193955). C.K.F. is supported by an Australian NHMRC Leadership Investigator Grant (GNT1172900). The authors gratefully acknowledge the contributions of the ACCESS team members and the ACCESS advisory committee members who are not co-authors of this article. We also thank all clinical services participating in ACCESS (accessproject.org.au) for their invaluable support. Additionally, we extend our gratitude to the Melbourne Sexual Health Centre and the Microbiological Diagnostic Unit Public Health Laboratory for collecting NG isolates and conducting antimicrobial susceptibility testing. We would like to express our special thanks to Professor Rebecca Guy and Sandra Johnson for their exceptional assistance with data collection.

Author contributions

Concept and design: L.Z., M.S., J.J.O., M.W.T., and H.L.; Acquisition, verification of data: H.L., M.W.T., C.K.F., B.P.H., and M.A.S.; Constructing the model: H.L., L.Z., and M.S.; Interpretation of the modelling results: H.L., L.Z., M.S., J.J.O., and M.W.T.; Drafting of the manuscript: H.L., L.Z., and M.S.; Critical revision of the manuscript for important intellectual content: L.Z., H.L., M.S., J.J.O., M.W.T., B.P.H., and M.A.S. All authors have read and approved the final manuscript.

Competing interests

M.W.T. reports speaker's honoraria and consulting fees from Gilead Sciences. All the other authors declared no conflict of interest.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-026-68561-7.

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Peer review information *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.